Original Article

Ultrasonic features of automated breast volume scanner (ABVS) and handheld ultrasound (HHUS) combined with molecular biomarkers in predicting axillary lymph node metastasis of clinical T1–T2 breast cancer

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Background: In the post-American College of Surgeons Oncology Group Z0011 trial era, clinicians are attempting to preoperatively evaluate axillary lymph node (ALN) status using ultrasound. However, the value of preoperative ultrasound examination remains uncertain. The study aimed to investigate the ultrasonic features of automated breast volume scanner (ABVS) and handheld ultrasound (HHUS), in combination with molecular biomarkers, to predict the risk of ALN metastasis (ALNM) in clinical T1–T2 breast cancer.

Methods: A retrospective case-control analysis was conducted on 168 patients with clinical T1–T2 breast cancer at Peking University First Hospital between January 2013 and August 2021. Preoperative ABVS and HHUS examinations were performed. According to the pathology results of the ALN, patients were divided into metastatic and nonmetastatic groups. Logistic regression analyses were used to analyze the ultrasonic characteristics of ABVS and HHUS on clinical T1–T2 breast cancer, and molecular biomarkers were incorporated to predict the risk of ALNM.

Results: Of the 168 patients, 88 (52.4%) had ipsilateral ALNM while 80 (47.6%) had no ipsilateral ALNM. The univariate analysis showed that shorter tumor-skin distance (P=0.011), the Adler blood flow grade of II–III (P=0.014), and larger tumor size on ABVS (P<0.001) were associated with ALNM. The multivariate logistic analysis showed that these three risk factors, including the tumor-skin distance [odds ratio (OR) =0.279; P=0.024], the Adler blood flow grade (OR =2.164; P=0.046), and the tumor size on ABVS (OR =1.033; P=0.002), were independent predictive parameters.

Conclusions: The tumor-skin distance, tumor size on ABVS, and Adler blood flow grade have diagnostic value for ALNM in clinical T1–T2 breast cancer.

Keywords: Breast cancer; ultrasonography; automated breast volume scanner (ABVS); handheld ultrasound (HHUS); axillary lymph node metastasis (ALNM)

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Introduction

According to the 2020 Global Cancer Statistics, female breast cancer has surpassed lung cancer in incidence, ranking first among all cancers worldwide (1), with a mortality rate of 6.9%, and thus represents a serious threat to women's lives and health. The detection of axillary lymph node metastasis (ALNM) is the most important prognostic indicator in determining the N staging and treatment of patients with breast cancer. At present, sentinel lymph node biopsy (SLNB) is the standard method for determining the staging of the axillary lymph node (ALN) (2). Patients with negative sentinel lymph nodes do not undergo ALN dissection to avoid postoperative complications caused by axillary surgery (3). Therefore, evaluating the ALNM of breast cancer for guiding multidisciplinary treatment decisions is now considered to be the key role of axillary imaging.

Ultrasonography is the preferred imaging method for evaluating breast tumors and ALN (4). However, handheld ultrasound (HHUS) is associated with certain disadvantages, such as operator dependency and nonstandardized image storage. The automated breast volume scanner (ABVS) is a three-dimensional ultrasound imaging technology developed for breast examination. Its fully automated, full-breast, and three-dimensional imaging features provide clinicians with a more reliable, comprehensive, and repeatable noninvasive imaging system that can overcome operator dependency. Previous studies have confirmed that ABVS is equivalent to magnetic resonance imaging in the ability to measure tumor size (5-7).

Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and the Ki-67 index (the percentage of cells that are positive for Ki-67 as determined by immunostaining of the primary tumor), which affect the biological behavior of breast cancer cells (8), are widely acknowledged to be predictive and prognostic molecular biomarkers of breast cancer (9,10). Of these, the Ki-67 index, as a proliferation and prognostic marker, has been associated with recurrence risk (3). However, few studies have examined the combination of molecular markers with the ultrasonic characteristics of ABVS and HHUS for evaluating the features of primary lesions in breast cancer and for further predicting ALNM. This study thus aimed to analyze the ability of the ultrasonic features in ABVS and HHUS in combination with molecular biomarkers to predict ALNM in clinical T1–T2 breast cancer. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-956/rc).

Methods

Patients

From January 2013 to August 2021, 168 patients with clinical T1–T2 breast cancer confirmed by core needle biopsy and surgery and who had undergone preoperative HHUS and ABVS at Peking University First Hospital were enrolled in the study. All patients underwent ipsilateral SLNB or ALN core needle biopsy and were divided into metastatic and nonmetastatic groups based on the pathological results of the ALN. Complete sonographic, clinical, and pathological data were collected for the study, and retrospective case-control analysis was performed. The Medical Ethics Committee of Peking University First Hospital approved the study, waiving the requirement for informed consent due to the retrospective nature of the design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (I) no clinical intervention (such as core needle biopsy and neoadjuvant chemotherapy) performed before patients underwent ABVS and HHUS examinations; (II) a solitary tumor; (III) a clinical stage of T1–T2; and (IV) complete ABVS, HHUS, clinical, and pathological data. Meanwhile, the exclusion criteria were as follows: (I) distal metastases; (II) multifocal or multicenter tumors; (III) bilateral breast cancer; and (IV) carcinoma *in situ* or mixed invasive carcinoma.

According to the inclusion and exclusion, 18 patients (32 breast lesions) were excluded while 168 patients (168 breast lesions) were included (*Figure 1*).

Apparatus and methods

The Acuson S2000 ABVS system (5–14 MHz; Siemens Healthineers, Erlangen, Germany) with a 14L5BV three-dimensional probe (frequency 5–14 MHz) with a flexible mechanical arm was used to scan the lateral, median, and medial views of the bilateral breast, and each side was

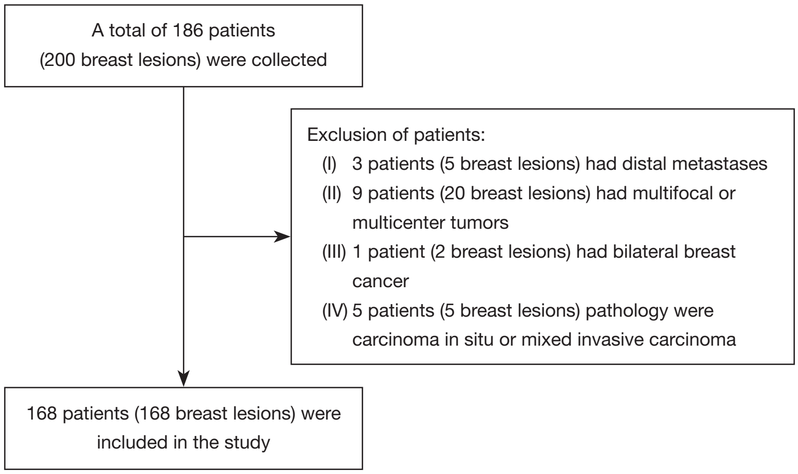

Figure 1 Flowchart of patient screening.

scanned three times. Subsequently, HHUS examination was conducted by two radiologists, with 6–18 MHz high-frequency linear transducers (18L6HD; Siemens Healthineers). After scanning, the obtained images were transmitted to the processing system and reconstructed in three dimensions by the workstation. The largest section was selected to measure the length, width, and height of breast lesions, and then the tumor volume was derived (length × width × height). The tumor-skin distance was defined as the vertical distance from the front edge of the tumor to the skin surface. The tumor-nipple distance was defined as the distance of the medial border of the tumor to the nipple. In ABVS, the reconstructed coronal-plane of breast lesions was observed for "convergence sign", the axial-plane and reconstructed sagittal-plane were observed for orientation (parallel to the skin, nonparallel to the skin), and posterior acoustic attenuation. All of the three planes were observed for microcalcification, shape [regular (oval, round), irregular], margin (circumscribed, noncircumscribed). Following this, a 18L6HD probe (frequency 6–18 MHz) was used in color Doppler flow imaging to determine the Adler blood flow grade (0–I, II–III). According to Adler blood flow grade (9), the blood flow signals were classified as follows: grade 0, absent flow signals; grade I, minimal, with 1–2 pixels of blood flow signals; grade II, moderate, with a main vessel and/or several small vessels; and grade III, marked, with 4 or more vessels visualized.

Sonographic data were independently analyzed and diagnosed by two radiologists with more than 5 years of working experience in an ultrasound department. Two senior radiologists with more than 15 years of work experience reviewed the reports. If there was a disagreement, a third radiologist with more than 15 years of experience was consulted to determine the final result.

Pathological results

The pathological results of breast cancer and the ALN were confirmed. The results of ER, PR, HER-2, and Ki-67 index were evaluated according to the immunohistochemistry. Positivity for ER or PR was defined as ≥1% of the tumor cell nuclei being immunoreactive (10), while positivity for HER-2 was defined as immunohistochemical staining 3+ or positivity in fluorescence *in situ* hybridization (11). The high status of Ki-67 was defined as ≥20% (12).

Statistical analysis

SPSS 26.0 software (IBM Corp., Armonk, NY, USA) was used to conduct statistical analysis. Continuous variables were tested for normality. Variables with a normal distribution are presented as the mean ± standard deviation, and the *t*-test was used to compare the two groups. Otherwise, the variables are expressed the median with interquartile range (IQR), with the nonparametric Mann-Whitney test being used for analysis. Categorical variables are expressed as the number of cases and percentage and were compared with the Chi-squared test or Fisher exact test. A P value <0.05 (two-sided test) was considered to indicate a statistically significant difference. Univariate and multivariate logistic regression analyses were used to screen the risk factors for predicting ALNM.

Results

After the inclusion and exclusion criteria were applied, 168 patients were enrolled in the study, with a mean age of 53.71±12.26 years (range, 23–87 years). Of these patients, 88 (88/168, 52.4%) had ALNM and 80 (80/168, 47.6%) did not. The mean age of the metastatic group was 51.56±10.40 years while that in the nonmetastatic group was 56.08±13.71 years (P=0.017).

The pathological types were analyzed, which indicated 148 (148/168, 88.1%) cases of invasive carcinoma of no special type (IC-NST), 15 (15/168, 8.9%) cases of invasive lobular carcinoma, 3 (3/168, 1.8%) cases of mucinous carcinoma, and 2 (2/168, 1.2%) cases of invasive micropapillary carcinoma.

We compared the metastatic group with the nonmetastatic group in terms of sonographic features and molecular biomarkers (*Table 1*). The mean tumor-skin distance in the metastatic group (0.50±0.29 cm) was shorter than that in the nonmetastatic group (0.62±0.32 cm), representing a statistically significant difference (P=0.011). ALNM was more likely to occur with breast cancer if the Adler blood flow grade was II–III (P=0.014). The median tumor size in the nonmetastatic group was 3.42 cm^3 (IQR 1.54–8.57 cm^3), while that in the metastatic group was 8.78 cm^3 (IQR 3.55–24.70 cm^3), representing a statistically significant difference (P<0.001). However, there were no significant differences in ER, PR, HER-2, Ki-67, tumor-nipple distance, convergence sign, microcalcification, margin, shape, orientation, or posterior acoustic attenuation between the two groups. The results are summarized in *Figures 2,3*.

Logistic regression analysis screened three independent risk factors for inclusion into the regression model: the tumor-skin distance [odds ratio (OR) =0.279; P=0.024], the Adler blood flow grade (OR =2.164; P=0.046), and the tumor size on ABVS (OR =1.033; P=0.002), (*Table 2*). The regression equation was as follows: Logit(P) = −0.198 − 1.275 × tumor-skin distance + 0.772 × Adler blood flow grade + 0.032 × tumor size on ABVS.

Discussion

The study showed that a smaller tumor-skin distance, a larger tumor size on ABVS, and the Adler blood flow grade of II–III were significantly associated with ALNM in clinical T1–T2 breast cancer and demonstrated certain clinical value in predicting the risk of ALNM.

HHUS is an important screening technique for breast examination and is widely used due to its noninvasiveness and convenience. However, HHUS is influenced by breast tissue elasticity and physician experience. In this regard, the objectivity and repeatability are relatively poor due to operator dependence, and measurement and evaluation are difficult to unify. ABVS is a technique that can effectively overcome these limitations. The image scanning of ABVS via a robotic arm provides standardization, with a minimum image layer spacing of 0.2 mm. Data measurements are then performed at the postprocessing workstation, where the three-dimensional reconstructed images can be zoomed and rotated, and the postprocessing workstation shows a minimum layer thickness of 0.5 mm, which makes ABVS one of the most reproducible measurement techniques (7,13). In addition, it allows for a retrospective review of the images after the ABVS examination has been obtained.

The tumor-skin distance is an independent predictor for ALNM, and a smaller tumor-skin distance is associated with a higher incidence of ALNM (14-16). This is consistent with the conclusion of this study. The tumor-skin distance in the metastatic group was 0.50±0.29 cm, which was significantly shorter than the 0.62±0.32 cm in the nonmetastatic group (P=0.011). Due to anatomy, there is abundant anastomosis between the subcutaneous and parenchymal lymphatic trunks and the breast skin, and the subcutaneous and parenchymal lymphatic trunks drain toward the axilla (17). The cutaneous lymphatic pathway is involved in the breast cancer ALNM pathway. Therefore, in assessing ALNM, the tumor-skin distance should be routinely measured. The tumor-skin distance can be a visualized as a quantitative parameter representing the infiltrative growth into the superficial fascial layer and even extending to the skin, with skin infiltration being an independent risk factor for ALNM.

The tumor-nipple distance is closely related to ALNM: the smaller the nipple-tumor distance is, the greater the risk of ALNM (14,18,19). However, Lewis *et al.* (20) suggest the opposite, reporting that the proximity to the nipple does not increase the risk of ALNM. Our findings are consistent with Lewis *et al.*'s study in that tumor proximity to the nipple was not associated with a higher incidence of ALNM. The branching and communicating lymphatic pattern, along with the corresponding superficial and deep lymphatic flow, suggest that the drainage to the ALN does not necessarily need to pass through the

Table 1 Comparison of the sonographic features combined with molecular biomarkers in the nonmetastatic group and metastatic group

Parameter	Nonmetastatic group (n=80)	Metastatic group (n=88)	P value
Age (years), mean ± SD	56.08±13.71	51.56±10.40	0.017
Tumor-skin distance (cm), mean ± SD	0.62±0.32	0.50±0.29	0.011
Tumor-nipple distance (cm), mean ± SD	4.31±2.51	4.09±2.50	0.556
Tumor size on ABVS (cm^3), median (interquartile range)	3.42 (1.54, 8.57)	8.78 (3.55, 24.70)	<0.001
ER, n (%)			0.800
Negative	26 (32.5)	27 (30.7)	
Positive	54 (67.5)	61 (69.3)	
PR, n (%)			0.760
Negative	30 (37.5)	31 (35.2)	
Positive	50 (62.5)	57 (64.8)	
HER-2, n (%)			0.280
Negative	61 (76.3)	73 (83.0)	
Positive	19 (23.8)	15 (17.0)	
Ki-67 index, n (%)			0.957
<20%	17 (21.3)	19 (21.6)	
≥20%	63 (78.8)	69 (78.4)	
Convergence sign, n (%)			0.156
Absent	31 (38.8)	25 (28.4)	
Present	49 (61.3)	63 (71.6)	
Microcalcification, n (%)			0.073
Absent	41 (51.3)	33 (37.5)	
Present	39 (48.8)	55 (62.5)	
Margin, n (%)			0.087*
Circumscribed	7 (8.8)	2 (2.3)	
Noncircumscribed	73 (91.3)	86 (97.7)	
Shape, n (%)			0.260*
Regular	5 (6.3)	2 (2.3)	
Irregular	75 (93.8)	86 (97.7)	
Orientation, n (%)			0.069
Parallel	52 (65.0)	45 (51.1)	
Nonparallel	28 (35.0)	43 (48.9)	
Posterior acoustic attenuation, n (%)			0.103
Absent	50 (62.5)	44 (50.0)	
Present	30 (37.5)	44 (50.0)	
Adler blood flow grade, n (%)			0.014
0–I	29 (36.3)	17 (19.3)	
II–III	51 (63.8)	71 (80.7)	

*, Fisher exact test. SD, standard deviation; ABVS, automated breast volume scanner; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

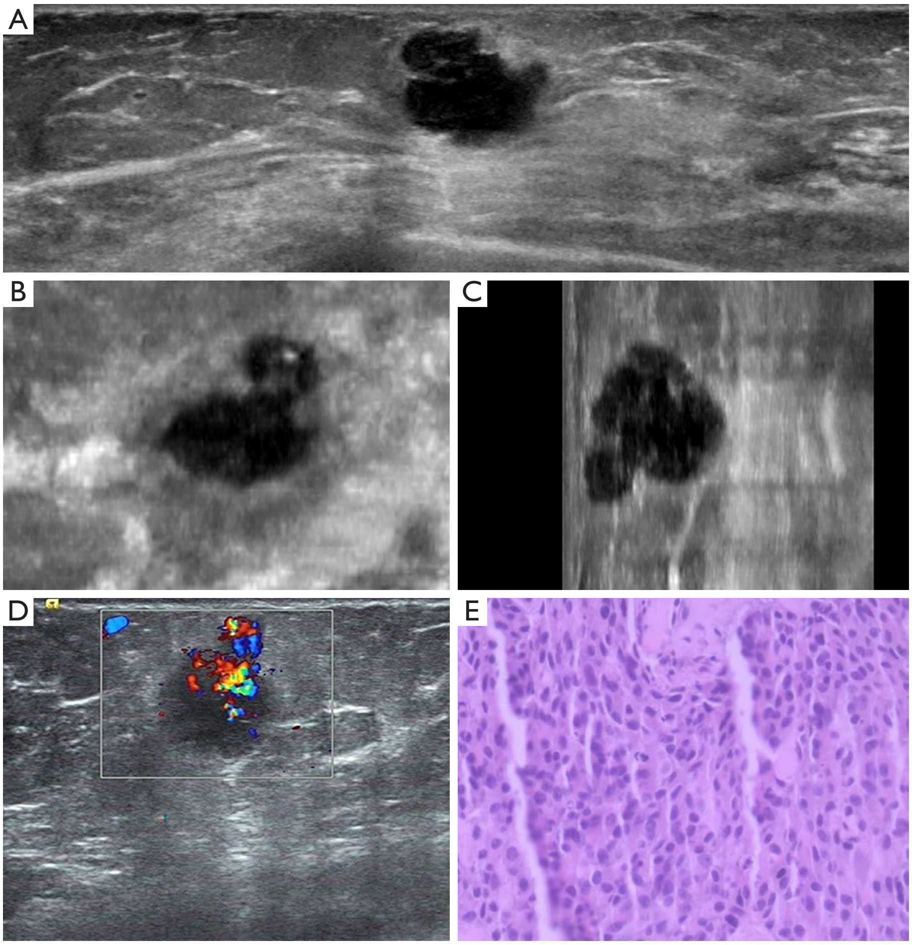

Figure 2 An 80-year-old woman confirmed with IC-NST and ALNM via pathology. (A) ABVS axial-plane sonography revealed a hypoechoic mass with an ill-defined margin. The tumor-skin distance was 2.0 mm. (B) ABVS reconstructed coronal-plane sonography indicated that the tumor-nipple distance was 10.0 cm, the tumor size on ABVS was 1.7 cm × 1.7 cm × 1.5 cm, and microcalcification was present. (C) ABVS reconstructed sagittal-plane sonography showed an irregular shape. (D) Adler blood flow grade III. (E) Histopathological examination confirmed IC-NST; immunohistochemistry indicated the following: ER negative, PR negative, HER-2 negative, and Ki-67 ≥20% (hematoxylin and eosin, 200×). IC-NST, invasive carcinoma of no special type; ALNM, axillary lymph node metastasis; ABVS, automated breast volume scanner; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

subareolar plexus (21).

Breast cancer with hypervascularity usually exhibits stronger invasiveness, which ALNM is prone to happen (22,23). The results of the study showed that tumors with Adler blood flow grade of II–III had a greater association with ALNM than did a grade of 0–I. It has been speculated that breast cancer is a vascular-dependent tumor, and its growth, invasion, and metastasis are closely related to vascularization. Although vascularization cannot directly lead to ALNM, the angiogenic factors produced by tumor cells can promote the formation of tumor blood vessels, thus enhancing the tumor cells' invasiveness. Tumor angiogenesis indirectly promotes ALNM.

The size of breast tumors is closely related to ALNM (23-27). In our study, the median volume of breast tumors was 3.42 cm^3 in the nonmetastatic group and 8.78 cm^3 in the metastatic group, representing a statistically significant difference. The larger the breast tumor is, the higher the risk of ALNM. This relationship may be explained by the following hypothesis: the larger the breast cancer is, the greater the possibility of infiltration to the surrounding lymphatic vessels, which ultimately leads to a higher risk of

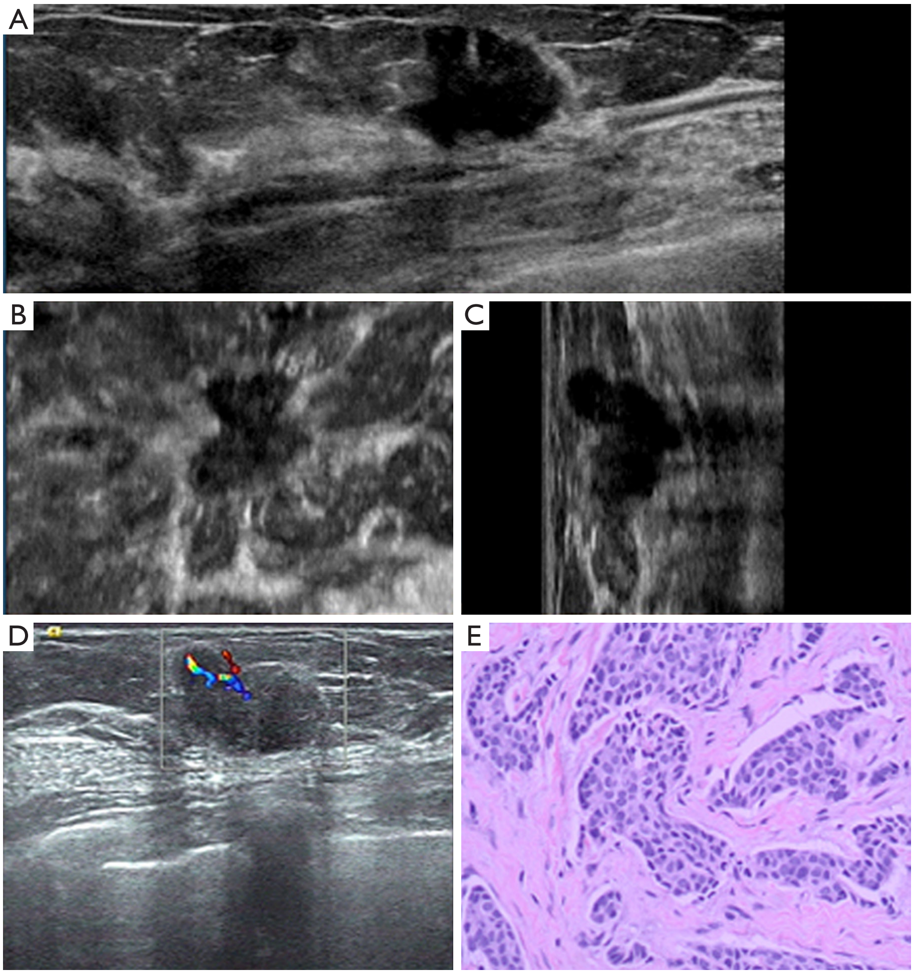

Figure 3 A 50-year-old woman confirmed with IC-NST and ALNM via pathology. (A) ABVS axial-plane sonography revealed a hypoechoic mass with a noncircumscribed margin and distortion of Cooper's ligament. The tumor-skin distance was 2.2 mm. (B) ABVS reconstructed coronal-plane sonography indicated that the tumor-nipple distance was 7.0 cm, the tumor size on ABVS was 2.4 cm × 1.8 cm × 1.6 cm, and convergence sign was present. (C) ABVS reconstructed sagittal-plane sonography showed an irregular shape. (D) Adler blood flow grade III. (E) Histopathological examination confirmed IC-NST; immunohistochemistry indicated the following: ER positive, PR positive, HER-2 negative, and Ki-67 ≥20% (hematoxylin and eosin, 200×). IC-NST, invasive carcinoma of no special type; ALNM, axillary lymph node metastasis; ABVS, automated breast volume scanner; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

Table 2 Logistic regression analysis for predicting breast cancer ALNM

Characteristics	Univariate analysis			Multivariate analysis		
	P value	OR value	95% CI	P value	OR value	95% CI
Tumor size on ABVS	0.001	1.036	1.014–1.059	0.002	1.033	1.012–1.054
Adler blood flow grade						
0–I	Ref	–	–	Ref	–	–
II–III	0.015	2.375	1.181–4.775	0.046	2.164	1.015–4.613
Tumor-skin distance	0.013	0.271	0.097–0.756	0.024	0.279	0.092–0.847

ALNM, axillary lymph node metastasis; OR, odds ratio; CI, confidence interval; ABVS, automated breast volume scanner; Ref, reference.

ALNM.

There is inconclusive evidence regarding the relationship between Ki-67 and ALNM. It has been suggested that a high Ki-67 index is an independent risk factor for ALN (28-30). However, some research does not support this, with Ki-67 being reported as incapable of predicting ALNM at initial diagnosis (31). In another study, Ki-67 ≥14% was not associated with a higher rate of SLN metastasis (P=0.403) (32). Moreover, it has been argued that support for Ki-67 as a prognostic indicator of node-positive breast cancer is based on limited samples and largely inferred from studies in which most patients had node-negative breast cancer (33). In our study, Ki-67 ≥20% was not predictive of ALNM and was not significantly associated with ALNM. There were 69 (69/88, 78.4%) cases with a high Ki-67 index in the metastatic group and 63 (63/80, 78.8%) cases with a high Ki-67 index in the no metastasis group. Presumably, these discrepancies can be attributed to different breast cancer T-staging and Ki-67 cutoff values leading to different outcomes.

There are some limitations to this study that should be addressed. First, we employed a single-center, retrospective design and a relatively small sample size, and thus a degree of selection bias might have been introduced. Second, the skin can be divided into the epidermis and dermis, which the study did not measure in detail.

Conclusions

ABVS and HHUS parameters demonstrated value in predicting the risk of ALNM in T1–T2 breast cancer. The smaller the tumor-skin distance, the larger the tumor size on ABVS, moreover, the Adler blood flow grade of II–III was found to be significantly related to ALNM. Radiologists should pay more attention to certain factors, including whether the breast cancer extends to the skin, the size of the tumor, and the blood supply.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-956/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-956/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Medical Ethics Committee of Peking University First Hospital approved the study, waiving the requirement for informed consent due to the retrospective nature of the design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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