Correlation of Automated Breast Volume Scanner Imaging and the Difference of Molecular Subtypes Between Core Needle Biopsy and Surgical Specimens

Dandan Wang
Jinling Hospital Affiliated Medical School of Nanjing University
Yating Li
Jinling Clinical Medical College of Nanjing Medical University
Hui Sun
Jinling Hospital Affiliated Medical School of Nanjing University
Chaoli Xu (sanyecao0104@163.com)
First Affiliated Hospital of Nanjing Medical University
Bin Yang
Jinling Hospital Affiliated Medical School of Nanjing University

Research Article

Keywords: Automated breast volume scanner, Breast cancer, Molecular subtype, Core needle biopsy, Surgical specimen

Posted Date: April 20th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1553451/v1

Abstract

Background: Core needle biopsy (CNB) and automated breast volume scanner (ABVS) play crucial roles in diagnosing breast cancer. However, the molecular subtype of breast cancer in CNB and surgery is a paradox at times. Analyzing the correlation between ABVS and the difference of molecular subtypes between CNB and surgery specimens has not been reported. The purpose of this study is to identify the characteristics of ABVS imaging that affect the discrepancy of molecular subtypes between CNB and surgical specimens in breast cancer patients.

Methods: Eighty-two breast cancer patients (83 lesions) who underwent ABVS examinations were enrolled at Jinling Hospital between November 2014 to October 2020. The molecular subtypes (luminal A, luminal B (HER-2 positive), luminal B (HER-2 negative), HER-2 overexpression, and triple-negative subtypes) and the discrepancy rate of the specimens via CNB and surgery were determined. The clinicopathological and ABVS imaging features were compared between the discrepancy group (molecular subtypes were different between CNB and surgery specimens) and the consistency group (molecular subtypes were concordant between CNB and surgery specimens). Receiver operating characteristic (ROC) curves were plotted for the diagnostic performance of the significant features.

Results: Of the 83 lesions, a concordance rate of 73.5% (κ=0.64) was shown between the CNB specimens and the surgical specimens for molecular subtypes. The presence of clear boundary, irregular shape, well-defined margin, and no retraction phenomenon on ABVS were independently associated with discrepancy in molecular subtypes (all $P < 0.05$). The area under the curve (AUC) for the combination of these four features on ABVS was 0.9 (95% CI:0.8-0.9), yielding a sensitivity and specificity of 100% and 41%, respectively.

Conclusions: ABVS is feasible with excellent sensitivity in determining the discrepancy of molecular subtypes between specimens via CNB and surgery. Multipoint puncture during CNB should be advocated for the lesions with the presence of clear boundary, irregular shape, well-defined margin, and lack of retraction phenomenon, thus leading to avoidance of discrepancy in molecular subtypes in clinical diagnosis and treatment processes in breast cancer patients.

Background

Breast cancer is a heterogeneous disease that differs in patients regarding its presentation, morphology, and response to chemotherapy[1]. According to the 2013 St.Gallen guidelines[2], breast cancer is classified into multiple distinct molecular subtypes (luminal A, luminal B, HER-2 overexpression, and triple-negative subtypes), and the different subtypes have different biological behaviors and prognoses [3, 4]. Correctly determining the molecular subtype of the lesion can provide reliable and timely information for clinical treatment.

Currently, the diagnosis of breast cancer is mainly based on the results of core needle biopsy (CNB) [5]. However, the pathological results of CNB specimens and surgical specimens are paradoxical at times,

ascribed to the difference in immunohistochemical detection indicators including sampling error, and tumor heterogeneous distribution [6–8]. At present, the analysis of the differences in the molecular subtypes and the related factors of the CNB and surgical samples is still limited[9]. Reducing the difference in the results of the molecular subtypes between CNB and samples after surgery will help improve the accuracy of the clinical diagnosis and will provide solid evidence for the following treatments.

Automated breast volume scanner (ABVS) is a three-dimensional technology that can scan the whole breast automatically and provide better visualization of the breast anatomy than handheld ultrasound[3]. More importantly, ABVS can identify breast cancer molecular subtypes according to the features including boundary, retraction phenomenon, and microcalcifications [3, 10–16]. For example, the retraction phenomenon, a feature that can only be seen on coronal planes, was the strongest independent predictive factor for the Luminal A subtype (OR = 9.06, P 0.001)[10]. Microcalcification and posterior tumor shadowing would be more frequently seen in the HER-2 subtype (AUC = 0.69, P 0.001)[11]. For the triple-negative (TN) subtype, the lesion would performed with a clear boundary, without retraction phenomenon or microcalcification(OR = 2.81, 5.88, 3.36, respectively, all P 0.05)[10]. Therefore, ABVS has become a promising modality to identify the molecular subtypes of breast lesions[3, 10–16]. However, using the characteristics of ABVS imaging to identify the discrepancy between CNB and surgical specimens has not been reported.

Therefore, the purpose of this study was to investigate the correlation of ABVS features with the discrepancy of the molecular subtypes between the CNB and surgical specimens.

Methods

Patients

From November 2014 to October 2020, 190 patients underwent ABVS examination at Jinling Hospital, with 108 patients were excluded. The inclusion criteria for this study were as follows: pathological results confirmed as malignancies; CNB was performed before surgery; breast cancer modified radical mastectomy was received; the molecular subtypes of CNB and surgical specimens were determined. Detailed exclusion criteria can be seen in the flowchart (Figure 1). Finally, 83 lesions from 82 patients (age range: 27-82 years, mean 50±10.8 years) were enrolled. The other clinical characteristics including menstruation, family history and pathological characteristics including tumor grade, TNM stage were recorded. This study was performed in accordance with the Declaration of Helsinki and was approved by Ethics Committee of Jinling Hospital. Since this is a retrospective study, the written informed consent was not required.

ABVS and data acquisition

ABVS was performed by using ACUSON S2000 system (Siemens Medical Solutions, Mountain View, CA, USA) equipped with a 14 MHz high-frequency linear transducer, which is capable of automatically acquiring complete images of the breast (17×15×6 cm^3, 318 two-dimensional slices). Patients were placed in the supine position with their arms above their head, and the examiners selected the most suitable settings for the patients based on their breast size (A-D and DD cups). Each breast was routinely scanned twice (medially and laterally). If participants had very large breasts, additional views were obtained to cover the entire breast. Coronal 3D images were already reconstructed before being sent to the diagnostic workstation.

Interpretation of the images included evaluating the size (largest diameter), boundary, shape, margin, microcalcification, retraction phenomenon, posterior acoustic features and hyperechoic rim according to BI-RADS for US (American College of Radiology.2003)[17]. The retraction phenomenon was defined as the convergence of cord-like hyperechogenicity intervals into a mass with hypoechogenicity on part or all of the coronal planes[15]. The interpretation was accomplished by two independent sonographers who had specialized in breast ultrasound for more than 5 years.

Biopsy methods

All CNBs were performed by ultrasound guidance (MyLab Twice, Esaote, Italy) under local anesthesia with automated biopsy gun (BARD, America) with an 18 Gauge(18-G), 16 cm long needle. Keep insert direction of the needle in the same plane as the sound beam during the puncture and the needle insertion angle is less than 30 degree. Considering the heterogeneous nature of the tumor, three needles were punctured in the tumor as evenly as possible in each specimen. All CNBs were completed by an ultrasonic doctor who specialized in breast CNB and had more than 5 years of experience.

Molecular subtypes analysis

An immunohistochemical analysis was used to evaluate both CNB specimens and surgical specimens to determine the estrogen- receptor (ER), progesterone- receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki-67 statuses of all of the patients. The molecular subtypes were determined to be luminal A, luminal B (HER-2 positive), luminal B (HER-2 negative), HER-2 overexpression, and triple-negative subtypes (TNBC) according to the 2013 St.Gallen guidelines [2]. The ER and PR statuses were defined as positive when more than 1% of the tumor cells were positive during the nuclear staining for either ER or PR[18]. HER-2 status was graded as 0,1+,2+, and 3+, was considered negative when the grade was 0 or 1+ and was considered positive when the grade was 3+. Fluorescence in situ hybridization was further performed for all of the tumors that were graded as 2+. We defined the samples as HER-2 2+ positive if the gene-to-chromosome ratio was more than 2.0[19]. The cutoff value of high Ki-67 expression was set as 14%.

Surgical method

All patients underwent modified radical mastectomy. Surgical specimens were analyzed by immunohistochemical. Molecular subtypes were determined according to the above criteria. Comparing with the CNBs, patients were divided into the discrepancy group (molecular subtypes were different between CNB and surgical specimens) and the consistency group (molecular subtypes were concordant between CNB and surgical specimens).

Statistical analysis

Cohen's Kappa statistics were used to interpret the agreement of the molecular subtypes between the CNB specimens and surgical specimens. A value of κ <0 suggested no agreement, a κ between 0-0.20 suggested a slight agreement, a κ between 0.21-0.40 suggested a fair agreement, a κ between 0.41-0.60 suggested a moderate agreement, a κ 0.62-0.80 suggested a substantial agreement, and a κ between 0.91-1.00 indicated an excellent agreement[20]. Student's t-test or chi-square test/Fisher's exact test was used to comparing the clinical features and ABVS imaging features with the molecular subtypes between the discrepancy and consistency groups. Receiver operating characteristic (ROC) curves were plotted for the diagnostic performance of the significant features. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. SPSS 21.0 (SPSS, Chicago, IL, USA) was used to perform the statistical analysis. Statistical significance was set to P 0.05 for all tests.

Results

Characteristics of patients and lesions

Most of the lesions were invasive ductal carcinoma and ductal carcinoma in situ both in discrepancy group (68.2% & 27.3%) and consistency group (75.4% & 19.7%) (Table 1). In the consistency group, 3 lesions were relatively rare pathological types, such as invasive lobular carcinoma (1.6%,1/61), invasive papillary carcinoma (1.6%,1/61) and mucinous carcinoma (1.6%,1/61). There were no significant difference between the two groups in pathological results (P 0.05) (Table 1).

The other pathological characteristics including histological grading, N stage, TNM of the tumors, and the clinical characteristics regarding patient age, menstruation, or family history were also summarized. However, these characteristics in our study were found no significant differences (all P > 0.05).

Table 1. Patient demographic characteristics between the two groups

	Discrepancy Group(%)	Consistency Group(%)	*t/ X²*	*P*
Ages	49±10.0	51±11.1	0.73	0.47
Menstruation				
Menopausal	8(9.8)	25(30.5)	0.19	0.66
Non-menopausal	14(17.1)	35(42.7)		
Family history				
Positive	2(2.4)	4(4.9)	-	0.66
Negative	20(24.4)	56(68.3)		
Histological grading				
I	2(2.4)	3(3.6)	1.18	0.83
II	13(15.6)	39(46.9)		
III	6(7.2)	17(20.5)		
NA	1(1.2)	2(2.4)		
N stage				
N0	10(12.0)	37(44.6)	2.69	0.62
N1	4(4.8)	7(8.4)		
N2	3(3.6)	7(8.4)		
N3	1(1.2)	4(4.8)		
Nx	4(4.8)	6(7.2)		
TNM				
I	5(6.0)	11(13.3)	2.40	0.82
IIA	8(9.6)	16(19.3)		
IIB	3(3.6)	13(15.7)		
IIIA	2(2.4)	8(9.6)		
IIIB	3(3.6)	6(7.2)		
IIIC	1(1.2)	7(8.4)		
Pathological results				
Invasive carcinoma	15(68.2)	46(75.4)	2.30	0.73
Ductal carcinoma in situ	6(27.3)	12(19.7)		

Invasive lobular carcinoma	1(4.5)	1(1.6)
Invasive papillary carcinoma	0	1(1.6)
Mucinous carcinoma	0	1(1.6)

Molecular subtypes

There were 22 lesions with differences in the molecular subtypes between the CNB and surgical specimen (donated discrepancy group) (Fig 2), and the rest of the 61 lesions were defined as the consistency group (Fig 3).

Among these 22 lesions, 6 (27.2%) lesions were classified as luminal A by CNB, 1 lesion was classified as luminal B (HER-2 positive) after surgery, and 5 lesions were classified as luminal B (HER-2 negative) (Table 2). Agreement of the molecular subtypes that were determined by both the CNB specimens and the surgical specimens reached a substantial agreement (κ 0.64, P 0.001) (Table 2)

Table 2. Agreement of molecular subtypes between the CNB specimens and surgical specimens

Molecular subtypes of the CNB specimens	Molecular subtypes of the surgical specimens							
		Luminal B				Agreement		
	Luminal A	Her-2(+)	Her-2(-)	HER-2	TNBC	(%)	κ	P
Luminal A	5(6.0)	1(1.2)	5(6.0)	0	0	73.5	0.64	0.001
Luminal B								
Her-2(+)	3(3.6)	27(32.5)	0	3(3.6)	0			
Her-2(-)	1(1.2)	2(2.4)	15(18.1)	0	0			
HER-2	0	2(2.4)	0	9(10.8)	2(2.4)			
TNBC	1(1.2)	0	1(1.2)	1(1.2)	5(6.0)			

TNBC: Triple-negative breast cancer subtype.

Comparison of ABVS features

The indistinct boundary, irregular shape, and spiculated margin occurred more frequently in the consistency group (53%,68.7% and 48.2%, respectively), while a clear boundary, an irregular shape, a lack of spiculated margin and retraction phenomenon were more presented in the discrepancy group (14.4%,19.3%,15.7% and 20.5%, respectively) (all $P < 0.05$). However, the largest diameter, posterior acoustic features, microcalcification and hyperechoic rim have no significant differences between groups (all P 0.05)(Table 3).

Table 3. Statistical results of ABVS imaging features between the two groups

	Discrepancy Group (%)	Consistency Group (%)	t/X^2	*P*
Size				
< 20mm	7(8.4)	17(20.5)	0.12	0.73
≥ 20mm	15(18.1)	44(53.0)		
Boundary				
Clear	12(14.4)	17(20.5)	5.06	0.02
Indistinct	10(12.0)	44(53.0)		
Shape				
Smooth	6(7.2)	4(4.8)	-	0.02
Irregular	16(19.3)	57(68.7)		
Posterior acoustic features				
Shadowing	8(9.6)	14(16.9)	1.51	0.47
Enhancement	2(2.4)	6(7.2)		
No changes	12(14.5)	41(49.4)		
Spiculated margin				
Present	9(10.8)	40(48.2)	4.07	0.04
Absent	13(15.7)	21(25.3)		
Microcalcification				
Present	10(12.0)	27(32.5)	< 0.01	0.92
Absent	12(14.5)	34(41.0)		
Retraction phenomenon				
Present	5(6.0)	29(34.9)	4.12	0.04
Absent	17(20.5)	32(38.6)		
Hyperechoic rim				
Present	8(9.6)	37(44.6)	3.84	0.05
Absent	14(16.9)	24(28.9)		

Diagnosis performance of significant features

ROC curves were plotted for these features, and we found significant differences and combinations of these characteristics (Fig 4). The AUROCs for irregular shape, clear boundary, well-defined margin, lack of retraction phenomenon, and the combination of these four features to more precisely ($P < 0.001$) in differentiating consistency and discrepancy were 0.60, 0.63, 0.62, 0.62 and 0.89, respectively. We also evaluated these features separately and in combination (Table 4), and the combination of these four features had high sensitivity (100%).

Table 4. The diagnostic performance of ABVS features in differentiating consistency and discrepancy lesions.

ABVS imaging features	AUC (95%CI)	Sensitivity	Specificity	PPV	NPV
Irregular shape	0.60 (0.46-0.75)	73%	7%	20%	40%
Clear boundary	0.63 (0.49-0.77)	45%	28%	19%	59%
Well-defined margin	0.62 (0.49-0.76)	41%	32%	18%	62%
Lack of retraction phenomenon	0.62(0.49-0.76)	23%	52%	15%	65%
Combined group	0.89 (0.81-0.96)	100%	41%	20%	71%
P value	<0.001				

*Combined group = combination of irregular shape, clear boundary, well-defined margin, and lack of retraction phenomenon.

Discussion

In this study, we found that a high discrepancy rate (26.5%) in molecular subtypes between CNB and surgery specimens were observed. Notably, ABVS imaging with specific features of clear boundary, irregular shape, well-defined margin, and lack of retraction phenomenon were significantly correlated with the discrepancy. Furthermore, the combination of these features yields an AUC of 0.9 and a high sensitivity of 100%. To our knowledge, this is the first report on the correlation of the ABVS imaging features with the difference in the molecular subtypes between the CNB and surgical specimens.

In our study, the agreement of the molecular subtypes between CNBs and surgical specimens had a substantial agreement. According to previously published studies, the concordance rate of the molecular subtypes between CNB and surgical specimen was ranged from 49.2% to 81.7%[7-9, 21]. Our research is within this range, indicating the reliability of our result. While the discrepancy may be mainly caused by the tumor heterogeneity. There have literatures been reported that the expression of ER at the edge of the lesion is significantly higher than in the center, while PR could be more heterogeneous distribution

compared with ER[7, 21]. Additionally, ER and PR had a negative correlation with HER-2[22]. As a result, ER, PR and HER-2 have a certain false negative rate and false positive rate in CNB. Some investigators found [23]that the false positive rate of ER, PR and HER-2 were 6.8%, 10.3% and 50.0%, respectively. And false negative rate for ER, PR and HER-2 were 26.5%, 29.6% and 5.4%. Therefore, the molecular subtypes of the CNB is inconsistent with the surgical specimen at times.

The results of our research show that the ABVS imaging features in the two groups had significant differences in the boundary, shape, spiculated margin, and retraction phenomenon. It is reported that of these four features, retraction phenomenon is mainly shown in the luminal A subtype which can be one the specific ABVS feature of the luminal A subtype[10]. Jiang and his colleague[24] found that retraction phenomenon was an independent predictor of smaller tumors, lower grade and positive ER or PR expression status. Considering that luminal A has a smaller size and lower grade than other subtypes[10] , it is not surprised that retraction phenomenon were associated with luminal A subtype. However, some investigators found that[10, 11, 25] for other subtypes, except luminal A, were lack of retraction phenomenon in lesions. In our study, the luminal A subtype changed (54.5%) more than the other subtypes after surgery. We hypothesize that the retraction phenomenon may affect the accuracy of CNB. For a lesion with retraction phenomenon, the surrounding glands are often more stretched, which increases the hardness of the breast and increases the difficulties of biopsy. Therefore, the false positive or false negative rate increases and the concordance rate decreases. Before and after the age of 50, in other word, hormones level of premenopausal and postmenopausal patients will change, which lead to the expression of ER and PR will also be greatly different.

In our research, we analyzed the clear boundary, irregular shape, well-defined margin, lack of retraction phenomenon and the combination of these four features. We found that the diagnostic performance of the combined group in differentiating consistency and discrepancy was much better than other features alone. Interestingly, those features were more commonly exist in benign instead of malignant lesions. However, we found that clear boundary, irregular shape, well-defined margin and lack of retraction phenomenon all had the higher abilities to differentiate the discrepancy of molecular subtypes. We thought there are several reasons to explain it. Firstly, a lesion with clear boundary, irregular shape, well-defined margin and lack of retraction phenomenon tend to be classified as triple-negative breast cancer (TNBC) subtype[10, 25]. However, the TN subtype has an aggressive nature, it progresses rapidly. During the period of CNB to the operation, it may cause the change in tumor phenotype. Secondly, according to the previous study, Ki-67 was related to lymph node metastasis and blood flow grading[22]. The high expression of Ki-67 often means the greatly aggressive behavior of tumor, such as the TN subtype. As we discussed before, the TN subtype would be misclassified as benign sometimes for it has clear boundary, irregular shape, well-defined margin and lack of retraction phenomenon. However, there was a report concluded that with longer surgery time interval, Ki-67 would be higher after CNB[26]. The increase of Ki-67 would affect the molecular subtype of lesions. Therefore, for patients with TN subtypes, it is necessary to be treated with a short surgery time interval to decrease the difference between CNB and the surgery. The combination of these four characteristics obtained a high sensitivity (100%) in differentiating the

discrepancy, while it also increased the false positive rate. We considered that improper operation and different locations where samples are collected may cause it.

However, there are several limitations to our study. Firstly, the patient populations in our study are relatively small, which may lead to deviation in the final results. Secondly, handheld ultrasound had not been joined to compare in this study. Last but not least, this is a retrospective study of a single-center lacking prospective data. Therefore, our results are needed to be confirmed by further large samples evaluation.

In conclusion, we should pay more attention to lesions with these features during the CNB process. We should be more cautious in reducing the error of the biopsy results and in improving the accuracy of molecular subtypes before and after surgery so that doctors can use the CNB results to give appropriate treatment. Meanwhile, we should also focus on avoiding unnecessary treatments when formulating treatment plans.

Conclusion

The presence of clear boundary, irregular shape, well-defined margin, and lack of retraction phenomenon on ABVS is correlated with discrepancy of breast cancer molecular subtypes between the CNB and surgery. Multipoint puncture during CNB should be advocated for the lesions with those features, thus leading to avoidance of discrepancy in molecular subtypes in clinical diagnosis and follow-up treatment in breast cancer patients.

Abbreviations

ABVS, automated breast volume scanner;

CNB, core needle biopsy;

ROC, receiver operating characteristic;

AUC, area under the curve;

AUROC, area under the ROC curve;

ER, estrogen- receptor;

PR, progesterone- receptor;

HER-2, human epidermal growth factor receptor 2;

PPV, positive predictive value;

NPV, negative predictive value;

TN, triple-negative subtype;

TNBC, triple-negative breast cancer.

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by Ethics Committee of Jinling Hospital and the written informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

DW analyzed and interpreted the patient data regarding imaging and clinical, and was a major contributor in writing the manuscript. YL acquired and analyzed the patient data regarding imaging, and made contributions in writing the manuscript. HS designed the work and acquired and analyzed the patient data regarding clinical. CX interpreted the patient data regarding imaging and clinical, and revised the work. BY designed the work and revised the work. All authors read and approved the final manuscript.

Acknowledgments

None.

References

1. Joseph C, Papadaki A, Althobiti M, Alsaleem M, Aleskandarany MA, Rakha EA. Breast cancer intratumour heterogeneity: current status and clinical implications. Histopathology.2018;73:(5).

2. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol.2013;24:(9).
3. Wang XL, Tao L, Zhou XL, Wei H, Sun JW. Initial experience of automated breast volume scanning (ABVS) and ultrasound elastography in predicting breast cancer subtypes and staging. Breast.2016;30.
4. Sachs N, de Ligt J, Kopper O, Gogola E, Bounova G, Weeber F, et al. A Living Biobank of Breast Cancer Organoids Captures Disease Heterogeneity. Cell.2018;172:(1–2).
5. Harbeck N, Gnant M. Breast cancer. Lancet.2017;389:(10074).
6. Asogan AB, Hong GS, Arni Prabhakaran SK. Concordance between core needle biopsy and surgical specimen for oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 status in breast cancer. Singapore Med J.2017;58:(3).
7. Chen X, Sun L, Mao Y, Zhu S, Wu J, Huang O, et al. Preoperative core needle biopsy is accurate in determining molecular subtypes in invasive breast cancer. BMC Cancer.2013;13.
8. Meattini I, Bicchierai G, Saieva C, De Benedetto D, Desideri I, Becherini C, et al. Impact of molecular subtypes classification concordance between preoperative core needle biopsy and surgical specimen on early breast cancer management: Single-institution experience and review of published literature. Eur J Surg Oncol.2017;43:(4).
9. Polcher M, Braun M, Tischitz M, Hamann M, Szeterlak N, Kriegmair A, et al. Concordance of the molecular subtype classification between core needle biopsy and surgical specimen in primary breast cancer. Arch Gynecol Obstet.2021.
10. Zheng FY, Lu Q, Huang BJ, Xia HS, Yan LX, Wang X, et al. Imaging features of automated breast volume scanner: Correlation with molecular subtypes of breast cancer. Eur J Radiol.2017;86.
11. Zhang L, Liu YJ, Jiang SQ, Cui H, Li ZY, Tian JW. Ultrasound utility for predicting biological behavior of invasive ductal breast cancers. Asian Pac J Cancer Prev.2014;15:(19).
12. Girometti R, Zanotel M, Londero V, Linda A, Lorenzon M, Zuiani C. Automated breast volume scanner (ABVS) in assessing breast cancer size: A comparison with conventional ultrasound and magnetic resonance imaging. Eur Radiol.2018;28:(3).
13. Xu C, Wei S, Xie Y, Guan X, Fu N, Huang P, et al. Combined use of the automated breast volume scanner and the US elastography for the differentiation of benign from malignant lesions of the breast. BMC Cancer.2014;14.
14. Golatta M, Franz D, Harcos A, Junkermann H, Rauch G, Scharf A, et al. Interobserver reliability of automated breast volume scanner (ABVS) interpretation and agreement of ABVS findings with hand held breast ultrasound (HHUS), mammography and pathology results. Eur J Radiol.2013;82:(8).
15. Chen L, Chen Y, Diao XH, Fang L, Pang Y, Cheng AQ, et al. Comparative study of automated breast 3-D ultrasound and handheld B-mode ultrasound for differentiation of benign and malignant breast masses. Ultrasound Med Biol.2013;39:(10).

16. Wojcinski S, Gyapong S, Farrokh A, Soergel P, Hillemanns P, Degenhardt F. Diagnostic performance and inter-observer concordance in lesion detection with the automated breast volume scanner (ABVS). BMC Med Imaging.2013;13.
17. Mendelson E, Baum J, Berg W, Merritt C, Rubin E, Merrit C. Breast imaging reporting and data system, BI-RADS: ultrasound2003.
18. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. Arch Pathol Lab Med.2010;134:(6).
19. Bartlett JM, Starczynski J, Atkey N, Kay E, O'Grady A, Gandy M, et al. HER2 testing in the UK: recommendations for breast and gastric in-situ hybridisation methods. J Clin Pathol.2011;64:(8).
20. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics.1977;33:(1).
21. Chen J, Wang Z, Lv Q, Du Z, Tan Q, Zhang D, et al. Comparison of Core Needle Biopsy and Excision Specimens for the Accurate Evaluation of Breast Cancer Molecular Markers: a Report of 1003 Cases. Pathol Oncol Res.2017;23:(4).
22. Zhao X, Yang X, Fu L, Yu K. Associations of Estrogen Receptor, Progesterone Receptor, Human Epidemic Growth Factor Receptor-2 and Ki-67 with Ultrasound Signs and Prognosis of Breast Cancer Patients. Cancer Manag Res.2021;13.
23. Seferina SC, Nap M, van den Berkmortel F, Wals J, Voogd AC, Tjan-Heijnen VC. Reliability of receptor assessment on core needle biopsy in breast cancer patients. Tumour Biol.2013;34:(2).
24. Jiang J, Chen YQ, Xu YZ, Chen ML, Zhu YK, Guan WB, et al. Correlation between three-dimensional ultrasound features and pathological prognostic factors in breast cancer. Eur Radiol.2014;24:(6).
25. Li Z, Tian J, Wang X, Wang Y, Wang Z, Zhang L, et al. Differences in Multi-Modal Ultrasound Imaging between Triple Negative and Non-Triple Negative Breast Cancer. Ultrasound Med Biol.2016;42:(4).
26. Chen X, Zhu S, Fei X, Garfield DH, Wu J, Huang O, et al. Surgery time interval and molecular subtype may influence Ki67 change after core needle biopsy in breast cancer patients. BMC Cancer.2015;15.

Figures

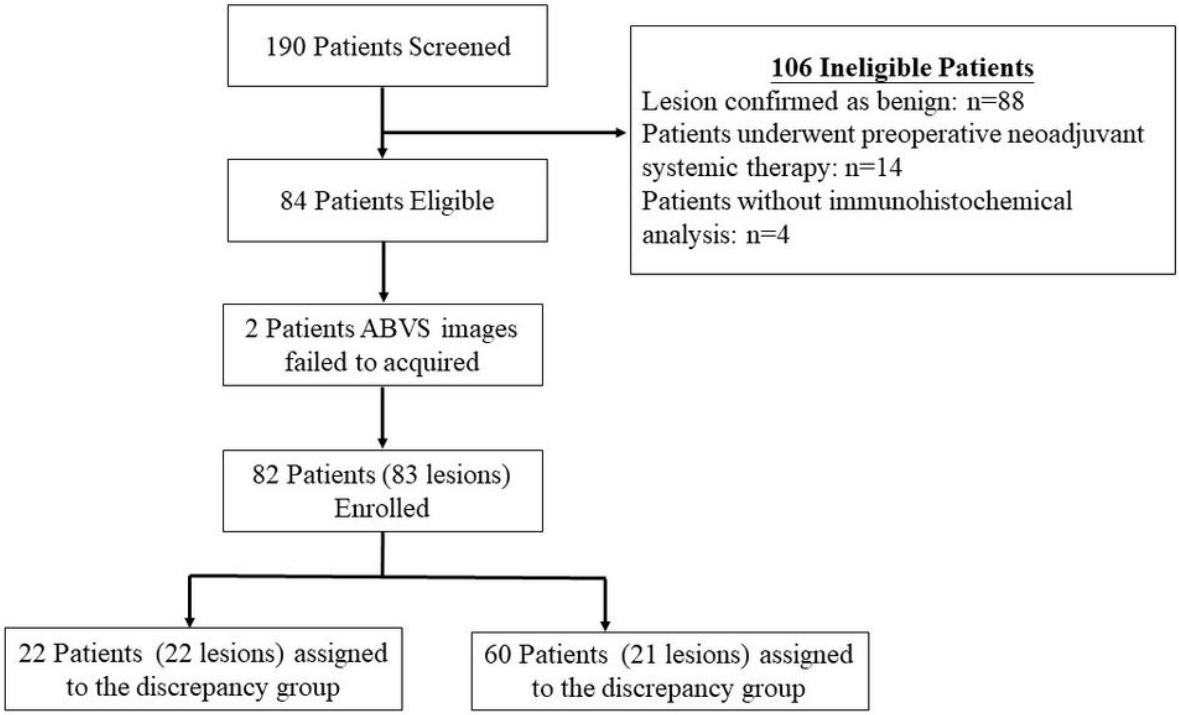

Figure 1

Detailed exclusion criteria.

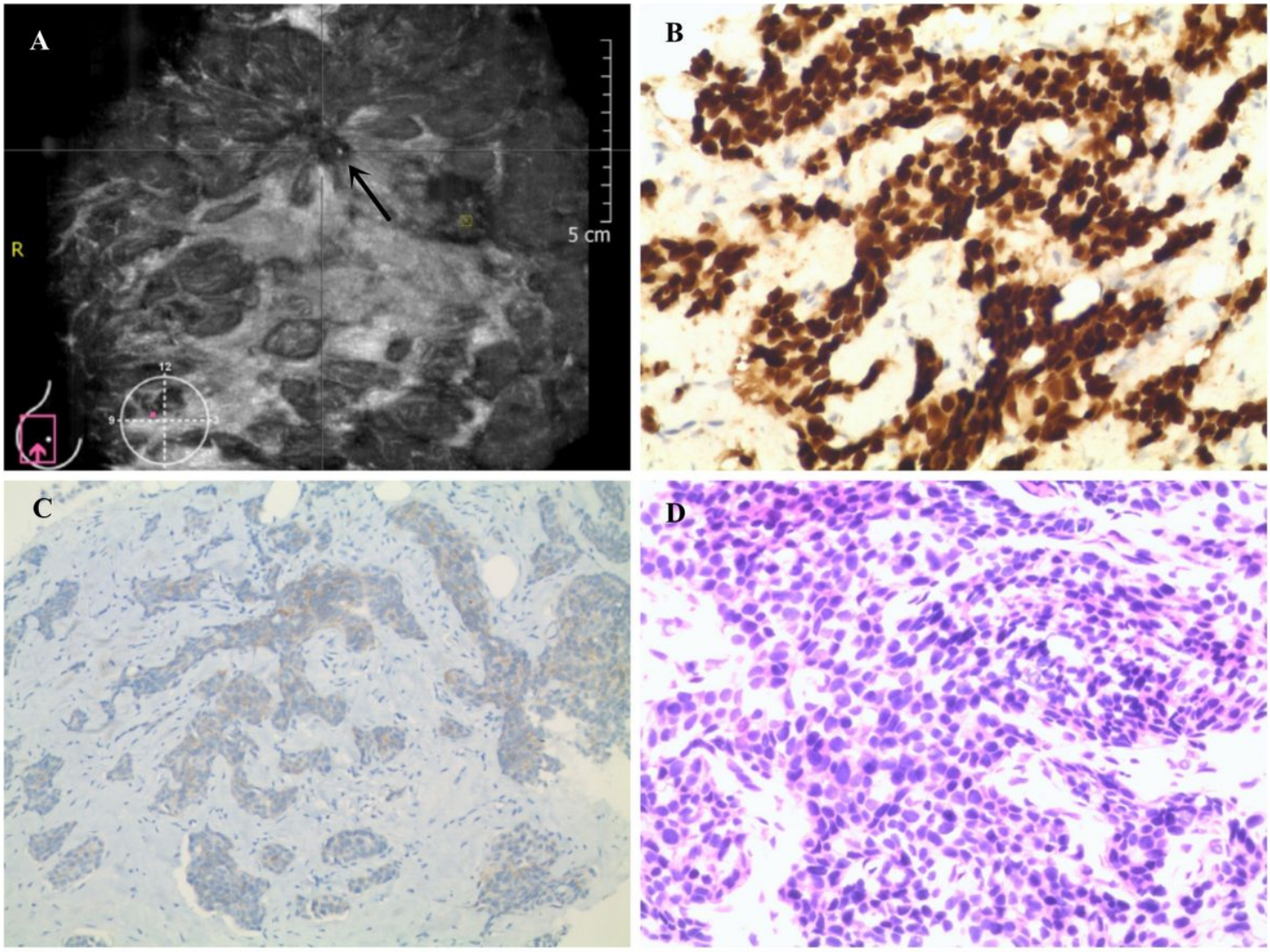

Figure 2

A 62-year-old woman of discrepancy group. A: ABVS image show microcalcification and tissues stretched. (arrow) **B:** ER in this lesion. **C:**HER-2 in the mass **D:**Hemotoxylin and eosin(H□E) image.

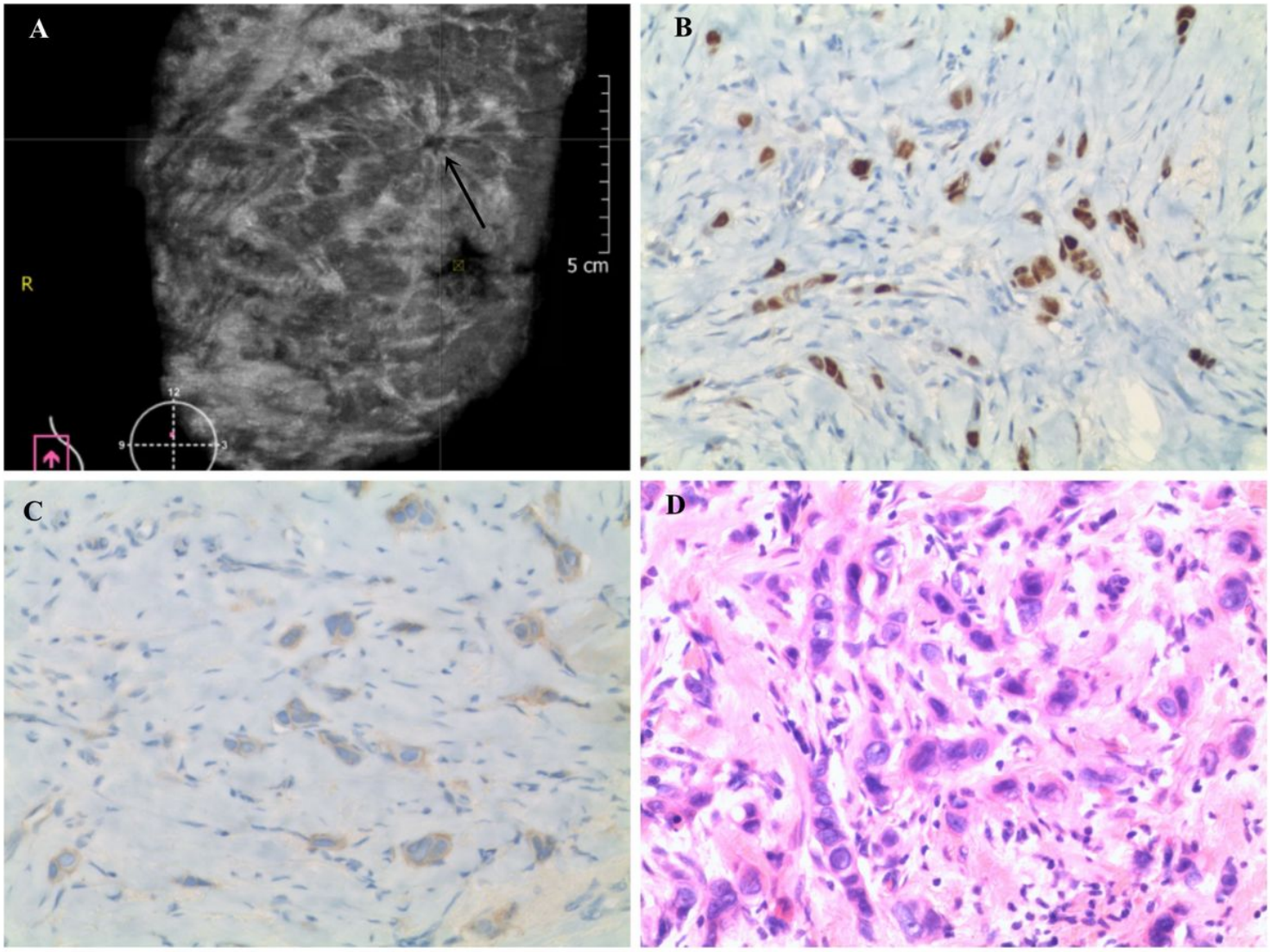

Figure 3

A 66-year-old woman of consistency group. A: ABVS image show spiculated margin and the retraction phenomenon(arrow). **B:**ER in this lesion. **C:** HER-2 in this lesion **D:** Hemotoxylin and eosin(H□E) image.

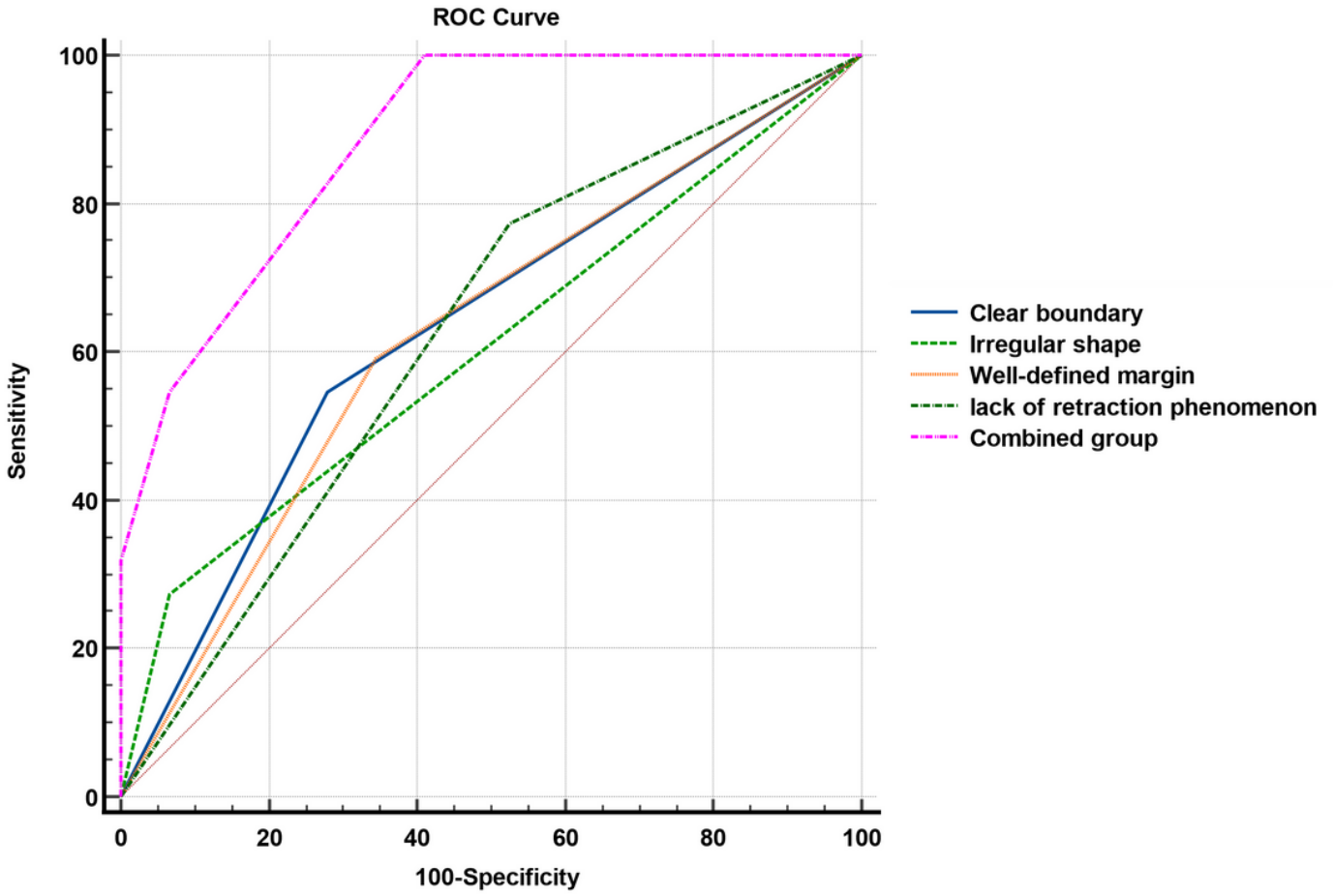

Figure 4

Areas under ROC curves of irregular shape, clear boundary, well-defined margin, lack of retraction phenomenon and the combination of these four characteristics.

*Combined group =combination of irregular shape, clear boundary, well-defined margin, and lack of retraction phenomenon.