

Factors that influence ultrasound evaluation of breast tumor size

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Abstract

Aims: To determine the factors influencing ultrasound breast tumor size assessment accuracy. **Material and methods:** Five factors (tumor type, molecular subtype, histological size, histological grade, and breast density) were used to assess the measurement accuracy of breast ultrasound in tumor size. Size underestimation was defined as ultrasound index lesion diameter < histological size by at least 5 mm. **Results:** Breast ultrasound underestimated tumor size significantly, especially in cases with intraductal components ($p=0.002$). There was a tendency for higher size underestimation in breast cancer tumors with high-histological grade ($p=0.03$), human epidermal growth factor receptor type 2 (HER2)-overexpressing breast cancer tumors ($p=0.02$) and hormone receptor (HR)-/HER2+ breast cancer tumors ($p=0.008$). Furthermore, core biopsy revealed higher probability of size underestimation with intraductal components ($p=0.002$). Size underestimation was more frequent with larger histological size ($p<0.001$). Masses in non-dense breasts were significantly underestimated ($p=0.036$) compared to dense breasts. **Conclusions:** The size underestimation was influenced by pathological type, molecular subtype, and histological size. The pathological results of core biopsy were conducive for predicting tumor size pre-surgery in precise breast cancer diagnosis.

Keywords: breast cancer; ultrasound; tumor size; molecular subtype; core biopsy

Introduction

Breast cancer is the most commonly diagnosed cancer in women. In recent years, breast-conserving surgery and minimally invasive treatment are becoming more appealing to women with early stage breast cancer [1]. Ul-

trasonography (US) is a traditional technique for imaging breast masses that is advantageous in terms of its safety and usability. US measurement of breast cancer tumor size is a routine pre-surgery examination. The accurate measure of breast cancer tumor size is a precondition for individualized treatment. Previous studies have reported that tumor type and histological size are the key components associated with underestimation of tumor size [2-6] and the gland density does not affect the US evaluation of tumor size [7]. It has reported that the maximal tumor diameter assessed by US is within 5 mm of the pathologic tumor size in 79.8% of cases [4].

The molecular subtypes of breast cancer and core biopsy are widely used in individualized therapy [8]. However, to our knowledge, the relationship between US measurement of tumor size and molecular subtyping or

Received 08.11.2018 Accepted 31.01.2019

Med Ultrason

2019, Vol. 21, No 2, 144-151

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the pathological results of core biopsy has not been reported.

In the present study, we enrolled a large population of patients with breast cancer to determine the factors that influence the accuracy of US breast tumor size assessment, especially the molecular subtyping.

Material and methods

Inclusion and exclusion criteria

We enrolled in this retrospective analysis 1028 patients with primary breast cancer who had underwent surgery in Jiangsu Breast Disease Center, the First Affiliated Hospital with Nanjing Medical University between January 2011 to June 2015. The study was approved by local Ethics Committee. The inclusion criteria were: 1) US and pathological information could be obtained and reviewed in the medical inquiry system; 2) no local treatment before surgery. The exclusion criteria were as follows: 1) neoadjuvant chemotherapy prior surgery; 2) multiple lesions that could not be distinguished in the US or pathological reports; 3) mass with inhomogeneous echo or microcalcification spots without low echo area. In figure 1 the flow diagram of analysis process is detailed.

Tumor size measurement in US

US was performed using a 3–14 MHz linear transducer (iU22; Philips Medical Systems, Bothell, WA, USA and MyLab Twice (Esaote S.p.A., Genova, Italy). Patients were required to lie in a supine position with their breasts exposed when the ultrasound was performed. All examinations and evaluations were made by a radiologist with more than 10 years of experience. A single low echo area was identified as the index lesion. Every controversial focus was diagnosed by two radiologists. The index lesion was sorted using the Breast Imaging Reporting and Data System (BI-RADS) and measured in three dimensions with US (fig 2). With the patient in the proper position, the radiologist scanned the breast in general to determine the location of the mass and the largest diameter of the tumor was measured, which was considered as the longest axis. The methods of the tumor size measurements are referred to in the previous study of our research group [1,9]. The halo or the edges of the speckles were included in the measurements of ultrasound [10,11]. If the observation error of three measurements was larger than 5 mm, the measurement was conducted and determined by another senior radiologist until the error was less than 5 mm. Then the three measures were averaged and a note as to the sonographic limits per lesion.

Classification of breast density

Mammography was performed using two digital full-field instruments (Senographe 2000D, GE, Fairfield,

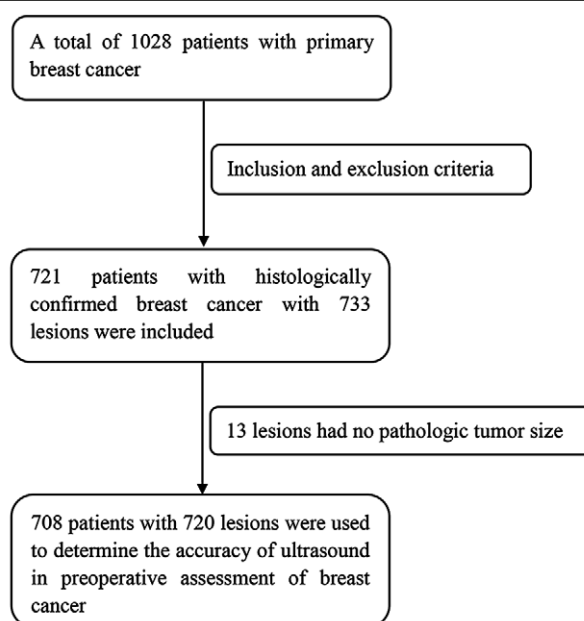


Fig 1. Flow diagram of screened and excluded patients

USA). The breast density was categorized according to the 4th edition of the BI-RADS proposed by the American College of Radiology (ACR). We divided patients into two groups according to different breast density, to evaluate if breast density was an influencing factor of US evaluation of breast tumor size.

Core biopsy

Core biopsy was performed with an automated Bard Magnum gun and a 14-gauge needle under ultrasound guidance. Based on the core biopsy pathological reports, the cases were divided into four groups: atypical ductal hyperplasia, pure ductal carcinoma in situ (DCIS), invasive carcinoma (IC, including pure IC [pIC] and a mixture of IC and DCIS) and other types.

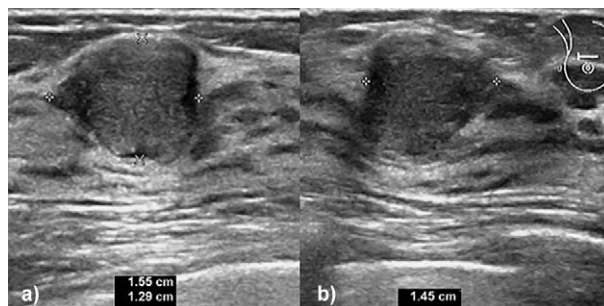


Fig 2. Ultrasonography (linear transducer with a frequency of 3–14 MHz) of a mass in 10 o'clock position in the right breast shows a hypoechoic irregular mass. The breast tumor size was measured in three dimensions: a) two major axes perpendicular to each other; b) the third major axis perpendicular to the previous two.

Tumor size measurement in pathology

After surgery, the breast specimen was sliced sequentially into 5 mm sections perpendicular to the long axis of the tumor involving the treated tumor and adjacent tissue. The pathological measurements were in terms of the microscopic borders of the tumors. The histological size was 5 mm \times number of slices containing tumor cells. The maximum dimension of the mass in US was compared with the largest diameter in histology.

Classification of postoperative pathological types

Based on the postoperative pathological reports, the tumor types were divided into four groups: ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) and other tumors (including mucinous carcinoma and papillary carcinoma). The IDC cases were divided into two groups: IDC with intraductal components (IDC+DCIS) and pure IDC. Hormone receptor (estrogen receptor [ER] and progesterone receptor [PR]) status, as well as human epidermal growth factor receptor type 2 (HER2) status, has guided breast

cancer subtype grouping. In this study, 638 cases with complete ER and PR status and HER2 expression level were divided into three classic groups: HR+HER2-/+ (ER+, PR-/+ , HER2-/+), HR-HER2- (ER-, PR-, HER2-), and HR-HER2+ (ER-, PR-, HER2+). The Scarff-Bloom-Richardson system was applied to classify the histological grade [12,13].

Definition of overestimation and underestimation

Size underestimation was defined as image index lesion diameter < histological size by at least 5 mm. Overestimation was defined as image index lesion diameter > histological size by at least 5 mm. The measurement was defined as precise when the deviation between image and histology was <5 mm.

Statistical analysis

Results were expressed as mean \pm standard deviation (SD). For all cases, the largest diameter of a tumor was used as the size reference in both the imaging and pathological reports. The mean difference between ultrasound and histology of the various groups was calculated, and

Table I. Correlation between the accuracy of ultrasound evaluation and pathological size. A difference between ultrasound and pathological size <5 mm was defined as accurate. A difference >+5 mm was considered overestimation and <-5 mm was considered underestimated.

Factor	Total	Accuracy of ultrasound measurement			p-value
		Underestimated	Accurate	Overestimated	
Total	720	191 (27%)	406 (56%)	123 (17%)	
Tumor type	720				0.002
DCIS	70	26	30	14	
Pure IDC	421	103	253	65	
IDC+DCIS	156	47	82	27	
ILC	14	10	4	0	
Other	59	31	10	18	
Histological grade	564				0.013
I and II	304	64	193	47	
III	260	83	140	38	
ER status	712				0.325
Positive	553	139	320	94	
Negative	152	47	79	26	
PR status	704				0.454
Positive	469	117	270	82	
Negative	235	69	128	38	
HER2 status	638				0.02
Positive	160	58	74	28	
Negative	478	111	291	76	
Ki-67	692				0.67630
Low	189	52	101	36	
High	503	133	286	84	
Molecular subtype	638				0.008
HR+HER2-/+	492	125	288	79	
HR-HER2-	89	20	57	12	
HR-HER2+	57	24	20	13	

HER2 – human epidermal growth factor receptor type 2; HR – hormone receptor; IC – invasive carcinoma; DCIS – ductal carcinoma in situ; IDC – invasive ductal carcinoma; ILC – invasive lobular carcinoma; ER – estrogen receptor; PR – progesterone receptor

the t-test was performed. Univariate analysis was carried out using the chi-square test or Fisher's exact test. In all cases, p-values were two-tailed, and p-values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (SPSS, IBM; Chicago, IL, USA).

Results

Overall performance

The 708 patients screened out from 1028 patients with 720 lesions were included to evaluate the accuracy of ultrasound in preoperative tumor size assessment of breast cancer.

The mean age of the included 708 patients was 51.80 years (median 50 years, range 25-93 years). The mean pathological tumor size was 23.4 ± 13.2 mm. The mean difference between the US and histological size was -2 mm ($p=0.002$). In Table I the number of different tumor type and accuracy of ultrasound measurement is detailed.

The mean breast cancer tumor size discrepancy of the pure IDC cases between US and histology was -1.6 mm (22.8 mm vs. 21.2 mm, $p<0.01$). The mean tumor

size discrepancy was -4.6 mm (25.5 mm vs. 20.9 mm, $p<0.01$) and -2.4 mm (25.5 mm vs. 23.1 mm, $p<0.01$) for the DCIS and IDC+DCIS cases, respectively. At -5 mm level, DCIS cases showed the highest ultrasound underestimation.

A total 564 IDC tumors (including pure IDC and IDC+DCIS) were divided into two groups according to histological grade. The mean size discrepancies in low and high histological grade compared with US were -0.99 mm and -3.02 mm, respectively ($p=0.003$). At -5 mm level, there were more underestimated cases in the high histological grade group than in the low histological grade group ($p=0.010$).

Table I lists the factors influencing misestimation. At ± 5 mm level, tumor type ($p=0.002$), histological grade ($p=0.010$), HER2 status ($p=0.02$) and molecular subtype ($p=0.008$) significantly influenced US measurement. There was no evidence that ER status ($p=0.325$), PR status ($p=0.454$), or Ki-67 value ($p=0.676$) could be used to predict US measurement alone.

As the largest group of breast cancer, the group of pure IDC was analyzed separately and this subgroup analysis suggested the same result. At ± 5 mm level, his-

Table II. Correlation between the accuracy of ultrasound evaluation and pathological size in the group of pure IDC. A difference between ultrasound and pathological size < 5 mm was defined as accurate. A difference > +5 mm was considered overestimation and < -5 mm was considered underestimated.

Factor	Total	Accuracy of ultrasound measurement			p-value
		Underestimated	Accurate	Overestimated	
Total	421	103(24.5%)	253(60.1%)	65(15.4%)	
Histological grade	394	101	238	55	0.048
I and II	208	43	136	29	
III	186	58	102	26	
ER status	415	100	252	63	0.871
Positive	314	74	193	47	
Negative	101	26	59	16	
PR status	415	100	252	63	0.915
Positive	265	62	162	41	
Negative	150	38	90	22	
HER2 status	392	94	243	55	0.025
Positive	79	27	39	13	
Negative	313	67	204	42	
Ki-67	412	101	246	65	0.712
Low	96	25	54	17	
High	316	76	192	48	
Molecular subtype	392	94	243	55	0.021
HR+HER2-/+	293	69	184	40	
HR-HER2-	70	13	49	8	
HR-HER2+	29	12	10	7	
Histological tumor size (mm)	421	103	253	65	
< 20	229	18	172	39	
20-50	181	74	81	26	
> 50	11	11	0	0	

HER2 – human epidermal growth factor receptor type 2; HR – hormone receptor; ER – estrogen receptor; PR – progesterone receptor

tological grade ($p=0.048$), HER2 status ($p=0.025$), and molecular subtype ($p=0.021$) significantly influenced ultrasound measurement (Table II).

US-guided core biopsy was performed in 489 of 720 lesions. Of the 489 lesions, 55 were atypical ductal hyperplasia. The remaining 434 lesions were divided into three groups: DCIS, IC, and other types. Of these, 52 lesions (11.98%) were DCIS; 376 cases (86.64%) were IC, of which 315 cases (72.58%) were pIC and 61 cases (14.06%) were IC with intraductal components (IC+DCIS). Six cases (1.38%) were other type (such as mucinous carcinoma). According to the ± 5 mm level, biopsy pathology reports indicated that breast cancer with a higher DCIS component was more likely to be underestimated, which was consistent with the results of the follow-up surgical pathological reports (fig 3). Given the limitation of tissue sampling in core biopsy, nearly half (25/52, 48.1%) of the DCIS cases were upgraded to invasive cancer after surgery. According to ± 5 mm level, the underestimated cases were 11/27 in DCIS, 14/25 in DCIS upgrade. The results show no difference in the accuracy of US between the DCIS group and the DCIS-upgrade group ($p=0.628$).

Impact of histological tumor size

The results comparing image size to pathological size of the different tumor staging are presented in fig 4. A total of 387 cases had tumor size <20 mm on US. The mean tumor size derived from ultrasound was 16.60 mm, while the mean histological size was 14.61 mm ($p<0.01$). In comparison to the overestimation of small tumors, US obviously underestimated tumor size in the patient group with higher stage tumors. The mean difference between US measured tumor size and pathological measured tumor size was -4.55 mm ($p<0.01$) and -33.61 mm ($p<0.01$) in group II (histological size between 20–50 mm) and group III (histological size >50 mm) tumors, respectively. Table III shows the consistency of US estimation when tumor pathological stage increased. US measurement tended to overestimate the size of small tumors while tending to underestimate the size of large tumors. According to the ± 5 mm level, ultrasound underestimated 33/387 cases (8.53%) in group I (histological size <20 mm), 135/309 cases (43.69%) in group II, and 23/24 cases (95.83%) in group III ($p<0.001$). In the subgroup analysis of pure IDC, ultrasound underestimated 18/229 cases (7.86%) in group I (histological size <20 mm), 74/181 cases (40.88%) in group II, and 11/11 cases (100.00%) in group III ($p<0.001$).

BI-RADS classification of breast tumors

Based on the BI-RADS classification, 518 tumors were divided into five groups. According to the ± 5 mm level, 3/8 (37.5%) BI-RADS 3, 19/48 (39.58%) BI-RADS

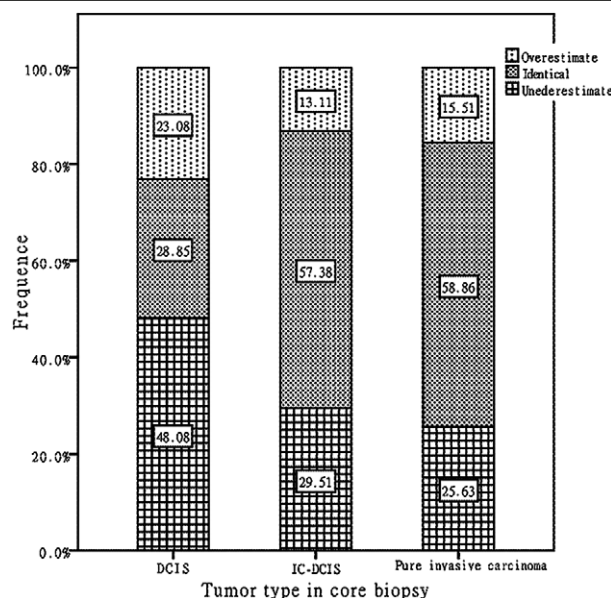


Fig 3. Percentage of underestimation in tumor types according to core biopsy results. According to the ± 5 mm level, the higher the DCIS component, the more likely it is to be underestimated ($p = 0.002$).

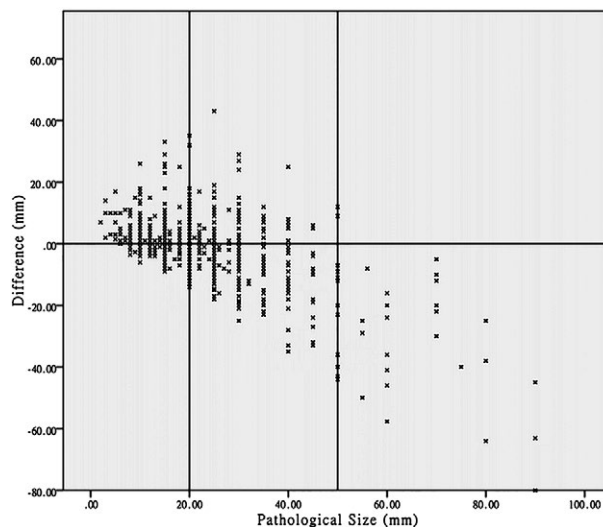


Fig 4. Scatter plot of the relationship between pathological size and difference between ultrasound and histology sizes for all tumors.

4A, 18/61 (29.51%) BI-RADS 4B, 38/193 (19.69%) BI-RADS 4C, and 50/208 (24.04%) BI-RADS 5 were underestimated. According to the ± 5 mm level, there was no significant difference between the BI-RADS 4B, 4C, and 5 groups ($p=0.387$). (Table IV).

Breast density

In this study, mammography was performed on 373 patients in our hospital. Masses in non-dense type (ACR

Table III. The accuracy of ultrasound evaluation in different groups of the histological size

Ultrasound size (mm)	Histologic size (mm)		
	≤20	20-50	≥50
≤20	301	101	6
20-50	84	198	14
≥50	2	10	4

1-3) breasts were significantly underestimated ($p=0.036$) compared to dense type (ACR 4) breasts (fig 5). Age and menopausal status, which are the factors that may affect female breast density, had no effect on the evaluation of ultrasonography accuracy.

Discussions

Methodologically, US is subjective to some extent. In addition, it is difficult to ensure that the measurement of pathological specimens is determined based on three-dimensional US measurements. To address these issues, in this study, every dimension of the exponential lesion was measured three times by the same radiologist to minimize the error. In the comparison of pathology and US results, the two largest diameters were chosen to partially reduce the non-correspondence of pathology and US results.

Regarding non-mass lesions, Yang et al [14] reported that US did not help to characterize the morphology or extent of calcification in symptomatic DCIS. In our study, non-tumor lesions showed microcalcifications and more frequently destroyed echoes of the gland under US imaging, which was related to the pathological type of DCIS.

In this study, the difference between US imaging and histology reports was -2 mm. The corresponding data in other studies were -8 mm and -4.2 mm, respectively [2,15]. A reduction in the underestimation of tumor size may be related to equipment upgrades. Another possible explanation is that, as a strong subjective test, US has been popularized in developing countries such as China in the past decades, enriching the experience of ultrasound doctors.

Regarding various tumor types, other studies have calculated linear regression between ultrasound measurements and pathological size of different tumor types, and

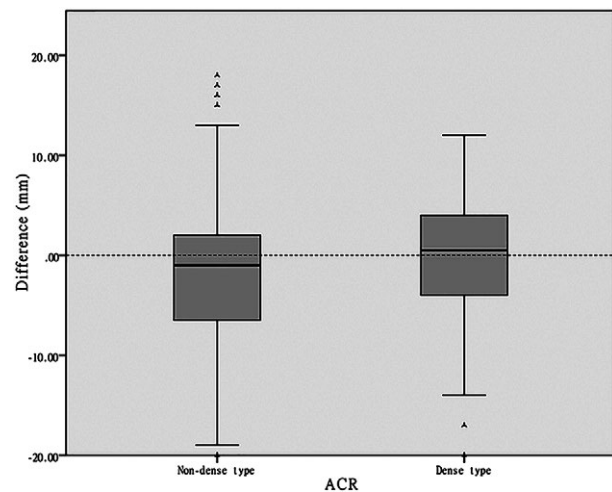


Fig 5. Masses in non-dense type (ACR 1-3) breasts were significantly underestimated compared to dense type (ACR 4) breasts.

ranked the degree of underestimation as $IDC < IDC+ILC < ILC$ [15]. We found that underestimation of size was common for DCIS components cases. Satake et al [16] attributed the size underestimation to deformation of the breast tissue larger than the caliber and the fibrosis around the catheter involved may cause structural distortion on the ultrasound. However, there was no significant difference in pathology and imaging for the ILC group. The likely cause may be that the sample size of this type of tumor in our study is small.

The assertion that histological grade is an independent prognostic factor dates back to 1991 [13]. However, few researchers have determined the relationship between histological grade and US imaging. In this study, high-grade malignancies were associated with underestimation of the severity of low-grade malignancies. Highly malignant tumors can cause irregular shapes and fuzzy echoes, which can adversely affect the measurement of tumor size.

Perou et al [17] referred to the concept of molecular subtype of breast cancer in 2000, which proved to be a milestone in the progress of breast cancer treatment. Studies have increasingly shown that molecular biological markers such as ER, PR, and HER2 are closely related to the biological characteristics of cancer. The main

Table IV. Correlation between the accuracy of ultrasound evaluation and BI-RADS category. A difference between ultrasound and pathological size < 5 mm was defined as accurate. A difference $> +5$ mm was considered overestimation and < -5 mm was considered underestimated.

Ultrasound classification (n=518)	Accuracy of ultrasound measurement			p-value
	Underestimated	Identical	Overestimated	
BI-RADS 3/4A (n=56)	22	29	5	0.011
BI-RADS 4B/4C/5 (n=462)	106	263	93	

goal of this study was to explore the accuracy of tumor size measurements in different molecular biology states. The results showed that the size of HER2+ cases was underestimated, but no similar phenomenon was found in ER+ or PR+ cases. Wojcinski et al [18] reported that HER2+ showed a high rate of structural deformation in surrounding tissues; this interpretation is consistent with our results. In clinical experience, breast cancer cases usually include three subtypes: cavity, HER2 overexpression and triple negative, although more detailed classification methods are gradually accepted. Our data indicate that the HER2 overexpression subtype clearly exhibits US underestimation compared to the other two subtypes. The underestimation of size can be attributed to the fuzzy boundary caused by the greater degree of HER2 overexpressing tumor infiltration. It was noted that HER2 positive was statistically significantly associated with tumor vasculature [19]. However, in some indicators related to prognosis or tumor cell biological behavior, the HER2 overexpression subtype is expected to fall between the other two subtypes, while the triple negative subtype is associated with a poor prognosis [20,21]. In addition, triple-negative breast cancer is not a single entity but a series of different diseases [22]. The heterogeneity of triple-negative breast cancer can explain the results to some extent. Due to the complexity of triple-negative breast cancer, a prospective study of the agreement between US features and molecular subtypes is expected.

As a common means of preoperative diagnosis, the 2015 European Society of Cancer Surveillance Breast Cancer Clinical Practice Guide [23] requires a core biopsy. There are differences in pathology reports between core biopsy and subsequent surgery. In addition, the pathology report of the core biopsy is important for selecting the appropriate surgical procedure. Based on the results of the core biopsy, we divided patients into three groups and obtained similar results. The DCIS components are also a key factor in underestimating the size. It is worth mentioning that core biopsy is susceptible to inherent sampling errors, resulting in underestimation [24]. We also studied the factors of pathological escalation and did not find evidence that the DCIS histological escalation of the core biopsy would lead to further underestimation of ultrasound imaging. Taking into account the above two points, we have reason to believe that the use of core biopsy pathology report will facilitate accurate measurement of tumor size before surgery. At the same time, due to the characteristics of DCIS, if the results of the core biopsy include DCIS components, we should use some other image examinations, such as magnetic resonance imaging (MRI), before breast-conserving surgery.

In addition to the pathological type, histological size is also a key influencing factor. For small lesions (<2 cm), we detected an overestimation of approximately 2 mm ($p < 0.01$). Pathological methods can explain almost indistinguishable deviations. Usually, the difference is small and may not have significant clinical value. However, we can conclude that tumor size is accurate or not underestimated in ultrasound examination. At the same time, as the size of histology increases, more sizes are underestimated. Others authors reported similar results [3,5]. Severe underestimation in large size cases may be associated with limitations of US probes and broader infiltration of advanced tumors.

BI-RADS classification is a recognized principle in the evaluation of breast lesions. Category 3 and 4A are often benign lesions. Interestingly, low-grade tumors (supposed to be breast cancer) were underestimated. A possible explanation is that some of the malignant features, including malignant halos, are ignored in these misdiagnosed cases.

Breast density has been reported to be associated with breast mass sensitivity in a mammography but not with US or MRI [7]. According to the fourth edition of BI-RADS proposed by ACR, this study classifies female breasts into four categories. In dense breast tissue (ACR 4), the extent of the disease is slightly too high and the size of the non-compact breast tissue (ACR 1-3) is underestimated. The reason for this difference is that various breast tissue densities exhibit different background imaging and affect the measurement of breast lesions. No significant differences were found when age and menopausal status were used as the basis for classification.

Limitations

Although the diameters were measured in three radial directions in both the US and pathological specimens, only the largest diameter was compared in this study. Therefore, in a few cases, the diameters of the US and pathological specimens become unequal. We tried to compare the dimensions by calculating the volume. However, since this is a retrospective study, it is no longer possible to accurately assess the irregular volume of a tumor. In addition, the US and pathology data for this large sample study were obtained by different radiologists and pathologists, although they were all senior doctors. In addition, pathological sampling methods still need to be improved. Finally, other factors may be related to the measurement of tumor size, such as whether a core biopsy was performed prior to surgery, and the stiffness of the tumor. Further prospective studies are necessary.

Conclusions

The use of US inevitably leads to an underestimation of the extent of the disease. Underestimated size is affected by pathological type, molecular subtype and histological size. The pathological results of the core biopsy help predict tumor size before accurate breast cancer diagnosis.

Acknowledgements

This work was supported in part by the National Natural Science Foundation of China (81572607, 81572595, 81502299, and 81502286); the Natural Science Foundation of Jiangsu Province (BK2011853, BK2011855 and BK20141023); the Program for Development of Innovative Research Team in the First Affiliated Hospital of NJMU (IRT-008) and a project Funded by the Priority Academic Program Development of Jiangsu higher Education Institutions (PAPD).

Conflict of interest: none

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