

Special Article - Breast Cancer

Similar Diagnostic Accuracy and Reproducibility of BI-RADS 4 and 5 Lesions in Radial and Meander-Like Breast Ultrasound

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Abstract

Breast ultrasound is crucial in the diagnostics of breast cancer. While meander-like Ultrasound (m-US) is most commonly used, radial Ultrasound (r-US) is emerging as suitable alternative. Breast lesions category BI-RADS 4 and 5 are suspicious and highly suggestive of malignancy, respectively, and mandate breast biopsy. We compare m-US and r-US in real-time with regard to diagnostic accuracy, examination time and the agreement in location, size and final BI-RADS classification of BI-RADS 4 and 5 lesions. Out of 1948 dual examinations (m-US and r-US), 57 lesions were classified as BI-RADS 4 or 5 either by r-US or m-US or by both scanning methods. For breast lesions category BI-RADS 4 or 5, sensitivity (both scan methods 94.1%), specificity (m-US 21.7%, r-US 39.1%), cancers missed rate (both 5.9%), accuracy (m-US 64.9%, r-US 71.9%), positive predictive value (m-US 64.0%, r-US 69.6%) and negative predictive value (both 100%) were similar. In m-US, the malignancy rate for category BI-RADS 5 was 93.8% versus for 50.0% for BI-RADS 4 whereas in r-US, malignancy rates were 88.2% and 58.6% for category BI-RADS 5 and 4, respectively. The examination was significantly shorter ($p < 0.01$) for r-US (13.6 minutes) compared to m-US (27.8 minutes). Our results support radial ultrasound as an alternative to meander-like ultrasound in breast lesions category BI-RADS 4 and 5 where patients benefit from a significantly shorter examination time.

Keywords: Agreement, BI-RADS 4 and 5, Diagnostic accuracy, Ductosonography, Examination time, Radial breast ultrasound

Abbreviations

US: Ultrasound; m-US: meander-like Ultrasound; r-US: radial Ultrasound; CI: Confidence Interval; ICC: Intraclass-Correlation; PPV: Positive Predictive Value; NPV: Negative Predictive Value

Introduction

Breast Ultrasound is a well-established and essential tool in the evaluation of breast lesions in daily clinical practice. The characterization and ultrasound classification of breast lesions follows the standardized recommendation of the BI-RADS Atlas [1]. The latter also provides clear recommendations on how to proceed for each BI-RADS category. Breast lesions category BI-RADS 4 are suspicious of malignancy and breast lesions category BI-RADS 5 are highly suggestive of malignancy. While in breast lesions category 4 and 5 histologic clarification by breast biopsy is indicated, a short term follow-up is proposed for BI-RADS 3 breast lesions (probably benign).

Most clinicians perform breast Ultrasound (US) by moving the probe in a meander-like pattern in two orthogonal planes. Even though Rosensweig introduced [2] radial ultrasound, also called ductosonography, already in 1982, it is seldom used as the sole ultrasound method in daily clinical practice. Radial Ultrasound (r-US) is usually performed as an adjunct to meander-like Ultrasound (m-US) in case of nipple discharge [3,4] or ductal abnormalities [5].

However, only in a few studies, radial scanning was performed [6-10]. A recent comparison of r-US and m-US showed that the diagnostic accuracy of the two scanning procedures is similar [11]. We and others have proposed r-US to be a viable alternative to m-US [12-14].

Real time scanning provides the opportunity for careful and thorough evaluation of breast lesions and permits detailed lesion analysis during the examination, which is a major advantage over retrospective analysis of static images on a screen [14]. Moreover, true comparison of lesion location, lesion size, examination time and most of all, the number of lesions missed by one examiner is only feasible by real-time scanning and assessment by different examiners.

Here, we compare for the first time the diagnostic accuracy, the examination time and the agreement in lesion localization, lesion size and final BI-RADS classification of real-time meander-like US and real-time radial US in regard to breast lesions suspicious and highly suggestive of malignancy mandating breast biopsy, i.e. BI-RADS category 4 and 5.

Materials and Methods

The single center study (Department of Obstetrics and Gynecology, University Hospital Basel, Switzerland) was approved by the local ethical committee and conducted from August 2011 to August 2014. Women from an unselected, consecutive, mixed collective who participated in this study signed an informed consent

form. Symptomatic women with breast pain or palpable breast lumps, asymptomatic women with increased risk for breast cancer or with dense breast tissue, and women with a personal history of breast cancer constitute the study group. An age younger than 18 years, a scheduled breast biopsy and male gender were exclusion criteria.

The examiners collected all demographic data including data on personal and family history, and performed a physical breast examination. Subsequently, each woman received a bilateral r-US and m-US in random order by two different examiners. Both examiners had access to the clinical and mammographic findings but not to the corresponding US assessment of the other examiner.

All examiners received a yearly training in breast US. In addition, the research fellow who performed all r-US underwent a theoretical and practical didactic training in r-US at the beginning of the study. M-US was carried out by experts or beginners under the supervision of an expert, as it is common in teaching hospitals.

Both US examinations (m-US and r-US) were performed with an ultrasound equipment of the same type (EUB-7500 V 16-53 Step 3.5, Hitachi Medical Systems Europe Holding AG, Zug, Switzerland). For m-US, a 50mm wideband, high frequency (13-5 MHz) linear transducer (EUP-L74M) was employed while r-US was carried out using a 92mm wideband (10-5 MHz) linear transducer (EUP-L53L) with a water standoff (a water-filled latex cover) according to the manufacturer's instructions. Both transducers had a center frequency of 7.5 MHz.

The duration of the US-examination was determined based on the timestamp on images taken at the beginning and at the end of the US-examination.

US-examinations were carried out as described in Jäggi et al. [11]. In brief, the women lied in an oblique supine position with her ipsilateral arm raised behind her head to flatten the breast tissue. For r-US, the examiner moved the transducer first clockwise around the mamilla in a radial and then in an anti-radial fashion, followed by a radial and anti-radial sweep of the upper outer quadrant to examine the axillary tail. In m-US, the transducer was moved in a meander-like pattern in vertical and transverse direction. Both r-US and m-US routinely included scanning of the axilla.

For both scanning methods, we measured the dimensions of each sonographic lesion on recordings in two orthogonal planes [11]. For each lesion the morphologic features were described and the lesions classified according to the BI-RADS Atlas [15] by the examiners. The location of each lesion was recorded according to the clock-face. In r-US, the mamilla is visualized as the rotation point which allowed for measuring the distance between lesion and nipple due to the wide probe whereas in m-US, the nipple-lesion distance was estimated. The shortest distance between lesion and skin was recorded in both US methods.

Breast lesions classified as BI-RADS 4 or 5 were biopsied for histological analysis.

Size, location, morphologic characteristics of the lesion and their final BI-RADS classification were electronically saved in the patient record (ViewPoint®, Version 5: GE Healthcare GmbH, Munich, Germany).

All data on patient and lesion characteristics extracted from the electronic patient records were entered into R (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org>) for further analysis.

Statistical methods

Patient and lesion characteristics were summarized. Categorical data are presented as frequencies and percentages. For continuous variables, mean and standard deviation as well as range are given.

Examination time was compared between m-US and r-US using a Wilcoxon signed rank test with continuity correction. For the assessment of diagnostic accuracy, histological results served as gold standard. Where lesions were missed by r-US or by m-US, the lesions were considered normal breast tissue and were interpreted accordingly for statistical analysis. For both methods, the sensitivity, specificity, and accuracy were calculated with 95% Confidence Intervals (CIs). The CIs were estimated according to Blaker. P-values were calculated using the exact McNemar's test. Positive and negative predictive values were calculated together with corresponding 95% CIs, and the respective p-values calculated. The negative predictive value was calculated either including or excluding missed cancers. Only lesions described by both methods were compared and used for p-value calculation.

For BI-RADS 4 and 5 breast lesions, the proportion of true positive, false negative, and cancers missed by one of the scan methods were calculated for malignant lesions. Correspondingly, the proportion of true negative and false positive, and the proportion of benign lesions not revealed were calculated for benign lesions. For data comparison between the two scan methods, an exact McNemar's test was used.

Lesions from the same subject were considered independent. All analyses were performed by R. No correcting for multiple testing was performed.

In categorical variables, agreement between the two scanning procedures was quantified using κ -values with quadratic weights. However, for the endpoint "clock-face location" the cyclicity was taken into account by choosing weights according to the distance on the clock rather than absolute timepoints, meaning that the distance between "0" and "1" and between "11" and "0" is 1 hour in both cases.

Weighted κ -values were interpreted as suggested by Landis: ≤ 0.20 poor agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.00 excellent agreement.

In continuous variables, the agreement was quantified using Intraclass-Correlation (ICC). The ICC is calculated based on analysis of variance. To this end, a mixed model is fitted to the data with scanning procedure and patient as random factors, and a fixed intercept was fitted. The ICC was estimated by dividing the variation related to the patient-to-patient difference by the total variance in the data. Therefore, ICC ranged between 0 and 1 and can be interpreted as the proportion of the variation of the data, which can be attributed to patient-to-patient variability. An ICC of 1 indicates a perfect agreement between r-US and m-US and that all differences

Table 1: Patient and lesion characteristics.

Patient characteristics		Lesion characteristics	
Number of patients	51 (100%)	Number of lesions	57 (100%)
Positive personal history	2 (3.9%)	Benign lesions	23 (40.4%)
Positive family history	17 (33.3%)	Fibroadenoma	5
Breast cancer	16	Fibrosis/sclerosis	11
Breast and ovarian cancer	1	Other B2 lesions	5
Mean age in years	56.4	B3 lesions	2
(min,max) [SD]	(30-86) [13.6]	Malignant lesions	34 (59.6%)
		DCIS	1
		Invasive lobular cancer	3
		Invasive ductal cancer	30

in the ratings are due to differences in the patients. For the variable “mean volume”, the data was cube-root transformed prior to fitting the model since the volume was estimated from the main axes and thus, any errors when measuring these axes were inflated, leading to outliers not acceptable in the mixed model.

ICC-values were interpreted according to Cicchetti: <0.40 poor agreement, 0.40-0.59 fair agreement, 0.60-0.74 good agreement, and 0.75-1.00 excellent agreement.

Results

In this study, we investigated the diagnostic accuracy of both scanning methods for sonographic breast lesions characterized as BI-RADS 4 or 5. Additionally, we analyzed the agreement of m-US and r-US with regard to size, location and morphologic characteristic of each breast lesion and compared the examination time for both scanning methods.

Out of 1984 dual US-examinations (r-US and m-US), 57 lesions from 51 patients were classified as BI-RADS 4 or 5 in either m-US or r-US or in both scanning methods. Corresponding patient and lesion characteristics are presented in Table 1. The patients were on average 56.4 years (30-86 years) old. The mean age of patients diagnosed with breast cancer was 58.0 years (30-79 years) and 53.8 years (30-86 years) for patients with a benign lesion ($p=0.07$). Two (3.9%) patients had a positive personal and 17 (33.3%) patients a positive family history.

Of the breast lesions classified as BI-RADS 4 or 5 in one or both scanning approaches, 27 (47.4%) were palpable. Breast cancer was diagnosed in 59.6% ($n=34$) of the lesions and 40.4% ($n=23$) had a benign histology (Table 1).

For BI-RADS 4 or 5 breast lesions both m-US and r-US had a sensitivity of 94.1%. The specificity for m-US was 21.7% and for r-US 39.1% (Table 2). Two cancers were missed by r-US but correctly identified by m-US. Two other cancers were missed by m-US but correctly identified by r-US. This corresponds to a cancer missed rate of 5.9% for either scanning method. Of the 23 lesions with a benign histology, 5 (21.7%) were correctly classified as BI-RADS 3 in m-US, and 8 (34.8%) lesions in r-US. In m-US 18 (78.3%) and in r-US 14 (60.9%) benign lesions were classified as BI-RADS 4 or 5. One (4.3%) benign lesion was missed in r-US, but none in m-US. As summarized in Table 2, sensitivity, specificity, accuracy, positive (PPV) and

Table 2: Diagnostic accuracy of m-US and r-US in BI-RADS 4 and 5 breast lesions.

	Meander-Like Ultrasound		Radial Ultrasound		
	n	%	n	%	
Malignant lesions	34	100	34	100	
Cancers identified	32	94.1	32	94.1	
True positive (BI-RADS 4 or 5)	32	94.1	32	94.1	ns
Cancers missed	2	5.9	2	5.9	
False negative* (BI-RADS 3)	0	0	0	0	ns
False negative* (BI-RADS 3 and missed cancers**)	2	5.9	2	5.9	ns
Benign lesions	23	100	23	100	
Benign lesions identified	23	100	22	95.7	ns
True negative (BI-RADS 3)	5	21.7	8	34.8	ns
Benign lesions missed	0	0	1	4.3	ns
False positive* (BI-RADS 4 or 5)	18	78.3	14	60.9	ns
False positive* (BI-RADS 4 or 5 and missed lesions**)	18	78.3	15	65.2	ns
Diagnostic Accuracy					
Sensitivity		94.1		94.1	ns
Specificity		21.7		39.1	ns
Accuracy		64.9		71.9	ns
PPV		64.0		69.6	ns
NPV (excluding missed cancers)		100.0		100.0	ns
NPV (including missed cancers)		71.4		81.8	ns

False negative and false positive were calculated excluding* and including** missed lesions.

PPV: Positive Predictive Value; NPV: Negative Predictive Value; ns: not significant

Negative Predictive Values (NPV) are similar for m-US and r-US.

The malignancy rate for lesions classified as BI-RADS 5 was 93.8% in m-US and 88.2 for r-US and for lesions classified as BI-RADS 4 50.0% for m-US and 58.6% for r-US (Table 3).

The dimensions of each lesion were measured in two orthogonal planes for both scanning methods. The mean maximal diameter and the calculated mean volume for r-US and m-US are listed in Table 4. The ICC values for the mean maximal diameter was 0.55 and for the mean volume 0.43, indicating fair agreement of these parameters between the two scanning procedures.

The location of each lesion as described by clock-face localization, and its distance to the mammilla and to the skin are presented in Table 4. The agreement in clock-face localization was excellent ($\kappa=0.89$) and for the mean distance to the mammilla (ICC 0.63) and to the skin (ICC 0.67) good.

For both US methods, each breast lesion was characterized according to the morphologic criteria described in the BI-RADS Atlas [15] and a BI-RADS category specified by the examiner. For breast lesions characterized as BI-RADS 4 or 5 in m-US or r-US or in both scanning methods, we found fair agreement in lesion orientation and echo pattern, moderate agreement in shape, posterior acoustic features, and tissue composition, and substantial agreement in lesion margin and breast density. The final BI-RADS classification moderately agreed (κ 0.51) for m-US and r-US (Table 5).

Table 3: BI-RADS classification by m-US and r-US related to malignant and benign histology.

	All lesions	Malignant lesions	Benign lesions
	n (%)	n (%)	n (%)
	57 (100)	34 (59.6)	23 (40.4)
Meander-like ultrasound			
BI-RADS 5	16 (100)	15 (93.8)	1 (6.2)
BI-RADS 4	34 (100)	17 (50.0)	17 (50.0)
BI-RADS 3	5 (100)	-	5 (100.0)
BI-RADS 2	-	-	-
Missed breast lesions	2 (100)	2 (100.0)	0 (0.0)
Radial ultrasound			
BI-RADS 5	17 (100)	15 (88.2)	2 (11.8)
BI-RADS 4	29 (100)	17 (58.6)	12 (41.4)
BI-RADS 3	7 (100)	-	7 (100)
BI-RADS 2	1 (100)	-	1 (100)
Missed breast lesions	3 (100)	2 (66.7)	1 (33.3)

Table 4: Agreement of size and location of BI-RADS 4 and 5 breast lesions.

	Radial US	Meander-like US	ICC	Weighted kappa	Agreement
Size					
Mean max. lesion diameter (mm) (min, max) [SD]	13.7 (3.5, 42.7) [9.3]	14.4 (5.00, 49.1) [9.3]	0.55		Fair
Mean volume (ml) (min, max) [SD]	1.4 (0.02, 14.6) [2.7]	1.7 (0.02, 20.2) [3.7]	0.43		Fair
Location					
Clock-face localization				0.89	Excellent
Mean distance to mamilla (mm)* (min, max) [SD]	28.0 (0.0, 86.0) [21.0]	35.2 (0.0, 100.0) [23.5]	0.63		Good
Mean distance to skin (mm) (min, max) [SD]	9.2 (2.0, 23.0) [5.1]	6.9 (2.0, 17.0) [3.6]	0.67		Good

The wide probe and the mamilla as rotation point enabled the measurement of the distance from the lesion to the mamilla in r-US which was estimated in m-US.

Table 5: Agreement between m-US and r-US with regard to morphologic description of BI-RADS 4 and 5 breast lesions.

	Weighted kappa	Agreement
Shape	0.44	Moderate
Orientation	0.24	Fair
Margin	0.64	Substantial
Echo pattern	0.30	Fair
Posterior acoustic features	0.41	Moderate
Tissue composition	0.48	Moderate
Breast density*	0.76	Substantial
Final BI-RADS classification	0.51	Moderate

*According to Madjar et al. [25].

The duration of the examination was timed and revealed a significantly shorter mean examination time for r-US (13.6 minutes) compared to m-US (27.8 minutes) (Table 6).

Discussion

The data of this study show a similar diagnostic accuracy of

Table 6: Examination time for m-US and r-US.

	Meander-like Ultrasound	Radial Ultrasound	p-Value
Mean examination duration (minutes)	27.8	13.6	<0.01
(min, max) [SD]	(4.7; 74.0) [17.3]	(3.9; 38.5) [6.3]	

m-US and r-US for lesions BI-RADS category 4 and 5. There was good agreement in lesion localization, fair agreement in lesion size and moderate agreement in final BI-RADS classification for the two scanning methods. However, examination time was significantly shorter in r-US compared to m-US.

Studies on m-US revealed malignancy rates for BI-RADS 5 lesions ranging from 57.1% [16] to 97.5% [17] and for BI-RADS 4 lesions from 8.6% [18] to 47.8% [19]. We found malignancy rates of 93.8% in m-US and 88.2% for r-US for BI-RADS 5 lesions, which for both scanning procedures is in the upper range of malignancy rates reported for m-US. In BI-RADS 4 lesions, our malignancy rates were 50.0% for m-US and 58.6% for r-US, each of which is higher than those reported in the literature.

For BI-RADS 4 and 5 lesions, we found the same sensitivity for m-US and r-US of 94.1%, and a specificity of 21.7% for m-US and 39.1% for r-US. Our findings are in line with Lee et al. [20] who reported a sensitivity of 98% and a specificity of 33% for m-US.

The PPV and NPV is 64.0% and 100.0% for m-US, respectively,

and 69.6% and 100.0% for r-US. Similar values of 65% for PPV have been reported for BI-RADS 4 and 5 lesions [19].

In our study, two breast cancers were missed by m-US and two different breast cancers by r-US. Both malignancies missed by one method were identified by the other method which results in a cancer missed rate of 5.9%. Each method detected 94.1% malignant lesions. For m-US, Berg et al. [21] reported that individual investigators detected between 49% and 66% of breast lesions, independent of BI-RADS classification.

The agreement of BI-RADS classification between m-US and r-US was moderate (κ 0.51). Similarly, moderate (κ 0.48) agreement for m-US was found in another study also reporting real time assessment [21]. Studies on retrospective evaluation of static m-US images revealed moderate (κ 0.45 - 0.56) [22,23] to substantial (κ 0.67-0.68) [23,24] agreement.

The agreement in regard to the morphologic description ranged from fair to substantial. We are not aware of any other study investigating the agreement of morphologic features in BIRADS category 4 and 5 breast lesions.

With an average examination time of 13.6 minutes, r-US in BI-RADS 4 and 5 lesions was significantly (<0.01) shorter compared to m-US (average examination time 27.8 minutes). We consider the wider probe used in r-US the main reason for the shorter examination time. To the best of our knowledge, data specifically addressing the examination times in breast lesions category 4 and 5 have not yet been published

The study design did not allow for the same examiner performing m-US and r-US which might be seen as a limitation. However, knowing the result of the initial US examination would have biased the second US examination. Furthermore, the individual experience of the examiner possibly had an impact on the examination time. However, US examinations performed by inexperienced examiners supervised by experts reflect a common situation in a teaching hospital. Most studies on agreement found in the literature are performed on retrospective analysis of static images. The main advantage of our study however, is that it was carried out in real time, i.e., two examiners evaluated the same lesions with the same type of US equipment.

Conclusion

In regard to breast lesions classified as BI-RADS 4 and 5, which always mandate a histologic clarification, radial ultrasound is a valuable alternative to meander-like ultrasound. The diagnostic accuracy of the two scanning methods is similar. However, the examination time is significantly shorter in radial ultrasound which is beneficial for patients, health care providers and institutions.

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