Ultrasound and MRI in the evaluation of mammographic BI-RADS 4 and 5 microcalcifications

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Microcalcifications are the common first sign of malignancy on mammography and present a diagnostic challenge. Biopsies of microcalcifications identified by mammography have a low positive predictive value due to the low specificity of mammography. Thus, a large proportion of biopsies of microcalcifications yield benign results, and so potentially could have been avoided. There is therefore a need for improved imaging of microcalcifications, but so far the roles of other imaging modalities such as ultrasound (US) and MRI have still not been clearly established.

This article summarizes the findings of a recent prospective study of the sequential use of mammography, US and MRI in the characterization of mammographic BI-RADS 4 and 5 microcalcifications. The results of this approach show an improvement in the characterisation of microcalcifications, with MRI being shown to have a negative predictive value of 100%. Thus, in this clinical setting MRI may be used to rule out malignancy, and could influence the decision about biopsy of the microcalcifications.

Microcalcifications account for 31% of all lesions detected at screening mammography [1,2]. Although they are easily detectable on mammography (MG), they however present a diagnostic challenge. The low specificity of mammography results in a low positive predictive value (PPV) — ranging from 21% to 42% — of biopsies of microcalcifications based on mammographic evidence [3–6]. In other words, a large proportion of biopsies of microcalcifications yield benign results, and so potentially could have been avoided [5[. However, a histopathologic workup of mammography findings of microcalcification is still considered essential for the establishment of a definitive diagnosis [7–9].

Due to considerable variability in its reported sensitivity, ultrasound (US) is not considered a reliable tool in the evaluation of microcalcifications [2,4,9–12] and a precise role for MRI has also still not been clearly established, although several studies have investigated the diagnostic performance of MRI in the classification of lesions identified on mammography as microcalcifications. However the results of such studies vary significantly [7,8,13–24]. The guidelines of the European Society of Breast Imaging (EUSOBI) state that the negative predictive value (NPV) of this use of MRI, reported to be around 70%, is insufficient to allow confident downgrading of lesions from suspicious to benign, and so to alter decisions about biopsy [7,8].

STUDY DESIGN

The aim of the current prospective study was to assess the diagnostic accuracies of US and MRI in the characterization of lesions that manifested as mammographic BI-RADS 4 and 5 microcalcifications. Women presenting with mammographic BI-RADS 4 and 5 microcalcifications and without any other associated mammographic findings were eligible for the study, The patients then underwent breast US, followed by breast MRI. Histopathologic diagnosis, obtained via US guided core-needle biopsy (CNB) or surgical excision, was set as reference standard. High-risk lesions obtained by CNB were confirmed by means of surgical excision. Patients having undergone CNB or surgical excision were examined at a 1-year follow-up with mammography, US and MRI.

The final study group consisted of 113 patients with 125 areas of suspicious microcalcifications.

METHODS

Mammograms were performed using a full field digital mammography system. Standard mediolateral oblique and craniocaudal projections were performed, with additional magnification views. US of both breasts was carried out using high frequency linear-array broadband transducers with a frequency of 9 - 14 MHz and 9 - 15

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MHz using either a Logiq 9 (GE Healthcare) or a Supersonic Aixplorer (SuperSonic Imagine) ultrasound system. US examinations were directed according to the mammographic estimation of the location of the microcalcifications.

US findings of the presumed area of mammographic microcalicfications were divided into two groups:

1) Visible changes

2) Invisible changes

The category of visible changes was further subdivided into:

a) microcalcifications (observed as hyperechoic dots) within hypoechoic area/mass or dilated ducts,

b) isolated microcalcifications, without associated findings,

c) other parenchymal changes (heterogeneous areas without significant hypoechoic area/mass or clearly visible microcalcifications).

Breast MRI was performed at 1.5 T (Magnetom Avanto, Siemens Healthineers) using a dedicated breast coil. The imaging protocol consisted of the following sequences:

Axial T2-weighted, sagittal T2W fast spin echo with fat saturation, axial T2W turbo spin echo, Axial T1-weighted three-dimensional (3D) gradient echo with fat saturation. Axial T1-weighted 3D gradient echo images without fat saturation were acquired before contrast administration. Dynamic 3D axial T1-weighted gradient echo images without fat saturation were then acquired five times for both breasts after the administration of a bolus of 0.1 mmoL/kg of a macrocylcic paramagnetic contrast agent (gadoterate meglumine, Dotarem). Unenhanced images were then subtracted from the contrast-enhanced images on a pixel-by-pixel basis.

CNB was performed after MRI, under US guidance, using a 14-gauge biopsy device (Monopty; Bard), with multiple passes per lesion. Mammography of the excised specimen was performed in order to confirm the presence of microcalcifications in the specimen.

In patients who underwent surgical excision of lesions, wire localization of the microcalcifications was performed under US guidance with the correct position being confirmed by mammography. For sonographically invisible lesions, mammography biopsy guidance was carried out using a fenestrated compression paddle with alpha-numeric grid.

Imaging findings were analyzed and reported using BI-RADS descriptors. BI-RADS category 1 – 3 were considered negative, while categories 4 and 5 were considered positive.

All clinical and imaging data were made available to the reading radiologist. Mammographic and MRI examinations were interpreted by one of three radiologists with 10 - 22 years of experience in breast imaging. Screening mammograms were evaluated by two radiologists independently and diagnostic mammograms by one radiologist. US exams and core needle biopsies were performed by the same clinician, who had 22 years of experience in breast imaging.

	malignant	benign	total	%	PPV3	p-value
US findings						<0.001
microcalcifications within hypoechoic mass, area or dilated ducts	35	17	52	41.6%	67.3%	
isolated microcalcifications	0	9	9	7.2%	0	
heterogeneous regions without mass or clearly visible microcalcifications	6	31	37	29.6%	16.2%	
negative (US invisible microcalcifications)	7	20	27	21.6%	25.9%	
total	48	77	125	100%		
US BI-RADS 1 – 3	7	51	58	46.4%		
US BI-RADS 4 – 5	41	26	67	53.6%		

Table 1. US features of mammographic BI-RADS 4 and 5 microcalcifications.

RESULTS

The prevalence of malignancy in our study group was 38.4%. Pure DCIS comprised 52.1% of malignant cases, microinvasive lesions a further 12.5%, and invasive lesions 35.4%.

Mammography as indicator for biopsy had an overall PPV3 (also known as the biopsy yield of malignancy or the positive biopsy rate) of 38.4%, while the mammographic BI-RADS 4 category had a PPV3 of 34.5%, and BI-RADS 5 a PPV3 of 88.9%.

Ultrasound results

Results of ultrasound examinations in the workup of microcalcifications are shown in Table 1 and Table 2. Changes associated with microcalcifications were seen on US in 78.4% of cases. Malignant microcalcifications were more likely to be visible on US (85.4%), compared to benign (74.0%). As shown in Table 2, malignant and benign microcalcifications presented differently on US, with statistically significant difference. Sensitivity, specificity, PPV3 and NPV for US were: 85.4%, 66.2%, 61.2%, and 87.9%. respectively.

MRI results

As for MRI, the sensitivity, specificity, PPV3 and NPV were 100%, 70.1%, 67.6% and 100% respectively. Although the estimated PPV3 for MRI was only moderate, it is still significantly improved compared

	US visible	US invisible	p-value
Histologic findings			0.18
malignant disease	41 (85.4%)	7 (14.6%)	
benign disease	57 (74.0%)	20 (26.0%)	
	98 (78.4%)	27 (21.6%)	
Mammographic BI-RADS category			0.2
MG BI-RADS 4	89 *(76.7%)*	27 *(23.3%)*	
MG BI-RADS 5	9 *(100%)*	0 *(0%)*	

Table 2. Correlation of sonographic visibility of microcalcifications with histologic findings and mammographic BI-RADS category.

	Malignant	Benign	Total	%	PPV3	P-value
MRI BI-RADS category						
MRI BI-RADS 1	0	0	0	0.00%	0	
MRI BI-RADS 2	0	21	21	16.80%	0	
MRI BI-RADS 3	0	33	33	26.40%	0	
MRI BI-RADS 4	8	21	29	23.20%	27.60%	
MRI BI-RADS 5	40	2	42	33.60%	95.20%	
Total	48	77	125	100.00%		
MRI morphology						<0,001
Mass	16	8	24	19.20%	66.70%	
Non-mass enhancement	32	41	73	58.40%	43.80%	
Focus	0	28	28	22.40%	0	
Total	48	77	125	100.00%		
MRI kinetic curve type						<0,001
Wash-out	29	8	37	38.10%	78.40%	
Plateau	17	17	34	35.10%	50.00%	
Persistent	2	24	26	26.80%	7.70%	
Total	48	49	97	100.00%		

Table 3. MRI features of pure microcalcifications and histopathology results.

to the PPV3 of mammography alone, which in our study was 38.4%. Published values [3–6] of the PPV3 of mammography range from 21% to 42%.

The approach used in our study, namely combining US and MRI as adjuncts to mammography alone in the work-up of microcalcifications, has so far not been published in the literature [7,8,13–23]. We believe that it was due to this multimodality approach that an MRI sensitivity of 100% could be obtained, with an NPV of 100%.

CONCLUSION

These results thus support the use of MRI for exclusion of malignancy in BI-RADS 4 and 5 microcalcifications, and allows the conclusion to be drawn that a negative MRI may influence a decision not to biopsy microcalcifications.

As shown in Table 3, non-mass lesion enhancement was the most common presentation of microcalcifications (58.4%). There was no statistically significant association between the lesion type (mass vs. non-mass lesions) and diagnostic accuracy. Sensitivity, specificity, PPV3 and NPV for masses were 100%, 50%, 80% and 100% respectively, and for non-mass lesions 100%, 53.7%, 62.6% and 100% respectively. However, masses had a higher probability of being malignant (PPV3 66.7%), compared to non-mass lesions (PPV3 43.8%).

When MRI BI-RADS descriptors were used in the analysis, there was a statistically significant difference between the presentation of malignant and benign microcalcifications.

As for the role of US in the assessment of microcalcifications, our results suggest that US alone cannot reliably exclude malignancy nor the need for biopsy of microcalcifications. However, the US presentations of benign and malignant microcalcifications were different [Table 1]: hyperechoic dots within a hypoechoic mass, area or dilated ducts were most often associated with malignancy, whereas isolated microcalcifications within normal breast tissue were seen only in benign cases. Also, as can be seen in Table 2, in our study, malignant microcalcifications were more commonly seen than benign microcalcifications (85.4% vs. 74.0%), a finding in agreement with other published studies [2,12,25]. This supports the presumption that recognition of different patterns of sonographic presentation of microcalcifications may influence the reading of MRI findings, and may improve MRI performance for microcalcifications.

LIMITATIONS

There are several potential biases which might have influenced our results, and further work is needed to validate our results. For example, we used US-guided CNB instead of vacuum-assisted biopsy (VAB), due to the work-flow set-up in our facility. We tried to minimize the impact of this by using a single, highly experienced radiologist with 22 years of experience in breast imaging, including US, to perform all US guided CNB; in addition, mammography examination of all biopsy specimens was carried out to confirm the presence of microcalcifications.

FUTURE STUDIES

Several future investigations are desirable. These include:

- Blinded MRI reading (i.e. without knowledge of prior US findings), to assess the exact influence of performing US prior to MRI on the final results of MRI.
- Interobserver variability tests for MRI results, to enable quantitative analysis of the effect of radiologist experience on the diagnostic accuracy of a method;
- Detailed analysis of influence of the different covariates on results (such as histologic diagnosis, breast density, patients hereditary risk for breast carcinoma, type of microcalcifications according to mammographic BI-RADS descriptors, etc).

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Representative case of combined US and MRI work-up of microcalcifications identified on mammography

The images below are a representative case of the sequential mammographical, US and MRI workup of microcalcifications. The histological-based diagnosis after second-look US guided CNB was atypical ductal hyperplasia. Wide surgical excision was recommended because of highly suspicious findings in MRI. Diagnosis after excision was multiple foci of DCIS, and because of the widespread area of non-mass enhancement seen on MRI, mastectomy was performed. The final diagnosis was microinvasive ductal carcinoma.

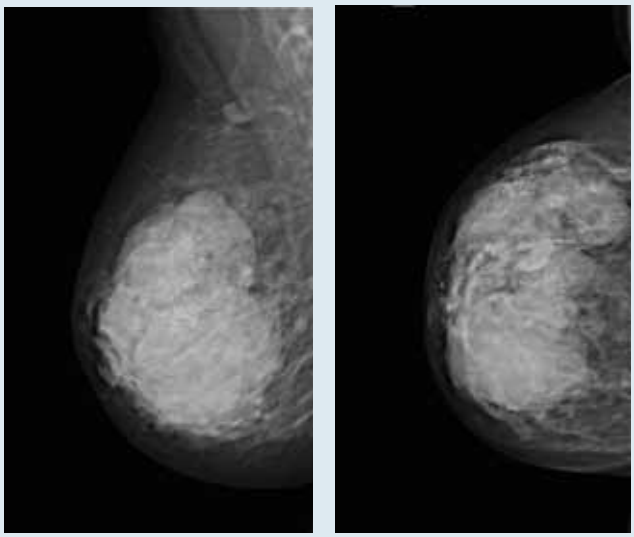


Figure 1a (Left Panel) and 1b (Right Panel) . Mammography, mediolateral oblique and craniocaudal projections: fine pleomorphic and linear branching microcalcifications, in segmental distribution, in the upper outer quadrant of the right breast. Multiple lobulated densities are seen in all quadrants.

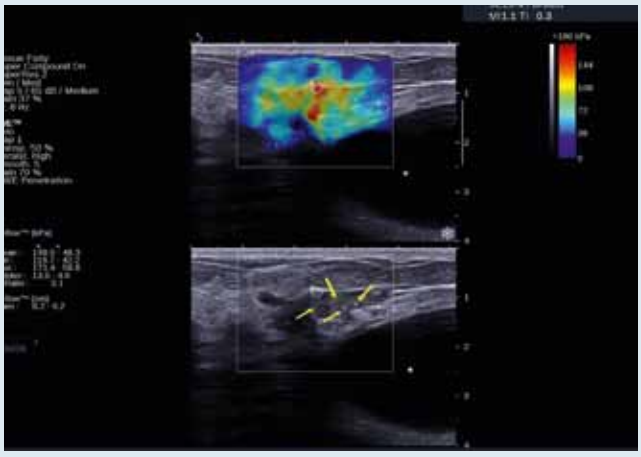
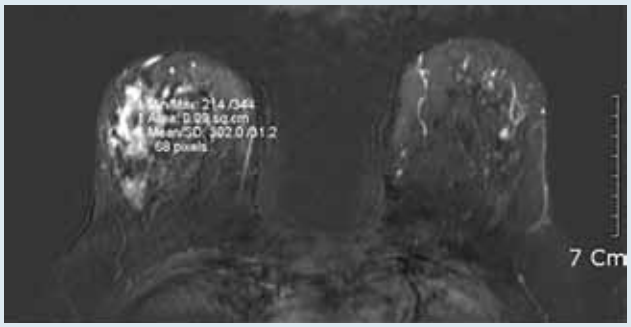


Figure 2. Ultrasound: microcalcifications were visible in B-mode as hyperechoic dots (yellow arrows) surrounded by heterogeneous irregular area. Multiple large cysts in all quadrants correlated to the lobulated densities visible on mammography.



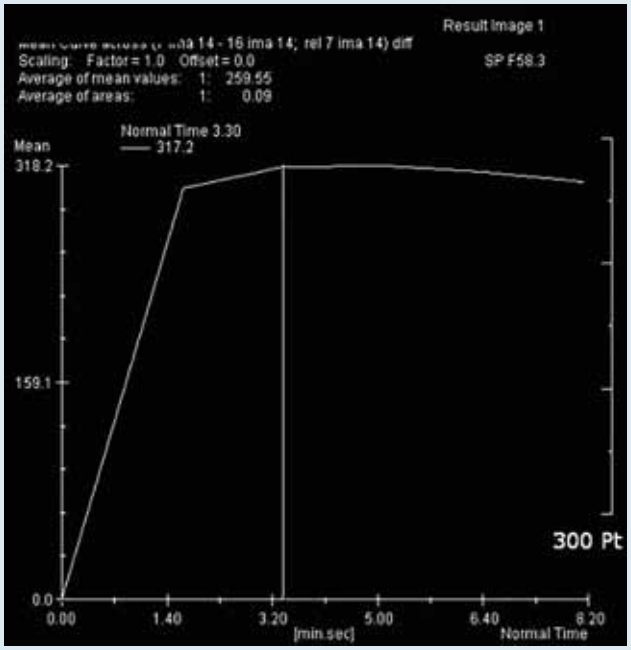


Figure 3a.(Top Panel) and 3b (Bottom Panel. Subtracted postcontrast MRI showed non-mass lesion of the right breast, with clumped internal enhancement and regional distribution. Dynamic-kinetic curve with ROI inside non-mass lesion had rapid enhancement in initial phase with plateau in the delayed phase. Second-look US guided core needle biopsy revealed atypical ductal hyperplasia. Suspicious imaging findings indicated wide open surgical excision - multifocal DCIS was revealed. Subsequent mastectomy was performed, and microinvasive ductal carcinoma was proven.