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

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PURPOSE
The aim of this study was to assess diagnostic accuracies of ultrasonography (US) and magnetic resonance imaging (MRI) in lesions that manifest as mammographic BI-RADS 4 and 5 microcalcifications, in the setting of conjoined use of mammography, US, and MRI.

METHODS
Patients with mammographic BI-RADS 4 or 5 microcalcifications, without additional findings, were included in this prospective study. All patients subsequently underwent breast US and MRI. Histopathologic diagnosis, obtained by US-guided core-needle biopsy or surgical excision, served as a reference standard. Diagnostic accuracies of US and MRI were calculated, and positive predictive value for different MRI BI-RADS imaging features were determined.

RESULTS
The study group consisted of 113 women with 125 areas of suspicious microcalcifications. MRI reached sensitivity, specificity, positive predictive value 3 (PPV3), and negative predictive value (NPV) of 100%, 70.1%, 67.6%, and 100%, respectively. Statistically significant differences in MRI morphologic features and kinetic enhancement curves were observed between malignant and benign microcalcifications. Sensitivity, specificity, PPV3, and NPV for US were: 85.4%, 66.2%, 61.2%, and 87.9%. There was statistically significant difference in presentation of malignant and benign microcalcifications at US.

CONCLUSION
In the setting of conjoined use of mammography, US, and MRI, MRI can reliably exclude malignancy in suspicious microcalcifications. Thus, negative MRI findings may influence the decision to biopsy the microcalcifications.

Microcalcifications account for 31% of lesions detected at screening mammography, and are often considered to be an early sign of breast cancer (1, 2). Although easily detectable on mammography, they present a diagnostic challenge. Most mammographic microcalcifications are currently assessed by means of histopathologic workup of percutaneous biopsy specimens - histopathologic proof is still considered essential for the definitive diagnosis (3–5). However, low specificity of mammography leads to low positive predictive value (PPV) of biopsies based on mammographic referral (ranging from 21% to 42%) (6–9). These data indicate that a large proportion of biopsies yield benign results and, therefore, potentially could be avoided (8). Breast Imaging and Reporting System (BI-RADS) is aiming to help stratifying the risk of malignancy, but BI-RADS descriptors are often not consistently applied between the readers, and PPV of mammography remains low (6, 10, 11).

Other imaging methods do not have a universally accepted role in the detection and characterization of microcalcifications yet (3, 7). Ultrasonography (US), due to considerable variations of reported sensitivities, is not considered a reliable tool in the evaluation of microcalcifications (2, 5, 7, 12–14). Also, the role of magnetic resonance imaging (MRI) is still not firmly established. Guidelines of the European Society of Breast Imaging (EUSOBI) claim that the negative predictive value (NPV) of MRI (reported to be around 70%) is not sufficient to confidently downgrade lesions from suspicious to benign, and alter the decision about bi-
Main points

• When mammography, US, and MRI are used in conjunction for the workup of BI-RADS 4 and 5 microcalcifications, MRI reaches 100% sensitivity, 70.1% specificity, 67.6% positive predictive value (PPV), and 100% negative predictive value (NPV). This means that negative MRI finding in such clinical setting may confidently rule out malignancy, and thus, influence the decision to perform biopsy of microcalcifications.

• When MRI BI-RADS descriptors are applied in analysis, microcalcifications present most commonly as non-mass lesions, with statistically significant difference in presentation of malignant and benign microcalcifications. Highest risk of malignancy is found for segmental distribution and clumped internal enhancement.

• US has shown clinically unacceptable values for test performance as a method for ruling out malignancy, with 100% sensitivity, 66.2% specificity, 61.2% PPV, and 87.9% NPV.

• In cases when microcalcifications are visualized with US (78.4% of cases in our study), there is statistically different presentation between malignant and benign microcalcifications. Thus, recognizing specific patterns of US presentation of malignant and benign microcalcifications may add additional value to the MRI performance. US finding of “hyperechoic dots within hypoechoic mass, area or dilated ducts” is most commonly related to malignancy, while finding of “isolated microcalcifications within normal breast tissue” is seen only in benign cases.

Methods

Study population

Eligible for this prospective study were women presenting with mammographic BI-RADS 4 and 5 microcalcifications, without associated mammographic findings. In further management, patients underwent breast US, followed by breast MRI. The histopathologic diagnosis, obtained by 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. The results of CNB and surgical excision were followed by 1-year follow-up with mammography, US and MRI. The study design and protocol were reviewed and approved by the institutional review board. All patients signed informed consent after the nature of the study had been fully explained to them.

In a period of three years 164 women were enrolled in the study. In the final data analysis, 51 women were excluded for the following reasons: 15 because mammograms were incomplete (only hard copies of film-screen mammograms from outside facilities were available to the readers, with MLO and CC projections, without spot compression views), 6 patients did not undergo US, 4 did not undergo MRI (2 refused because of claustrophobia, 2 had technical contraindications – 1 pacemaker, 1 ferromagnetic metal foreign bodies), 10 had no histopathologic diagnosis (did not complete workup in our institution), and 16 cases were lost from follow-up. The final study group consisted of 113 patients with 125 areas of suspicious microcalcifications (age range 36–71 years, median 55 years).

Imaging methods

Mammograms included in the study had to be performed using a full field digital mammography system (76 were performed in our department, using Mammatom Novation DR Siemens). Standard mediolateral oblique and craniocaudal projections, with additional magnification views were performed. In 37 cases where no magnification views were available, electronic magnification (zooming) of digital mammograms was used at the viewing workstation.

US of the breasts was performed using high frequency linear-array broadband transducers with a frequency of 9–14 MHz and 9–15 MHz (Logiq 9, General Electric Healthcare, and Supersonic, Aixplorer® ultrasound system, SuperSonic Imagine). US examination was directed based on the mammographic estimation of the location of microcalcifications. US findings of the presumed area of mammographic microcalcifications were divided into groups of 1) visible changes, and 2) invisible changes. Visible changes were 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 hyperechoic area/mass or clearly visible microcalcifications).

Breast MRI was performed at 1.5 T (Magnetom Avanto, Siemens). A dedicated breast coil was used, with the imaging protocol consisting of following sequences: axial T2-weighted TIRM (TI: 150.0 ms, TR: 4330.0 ms, TE: 69.0 ms, slice thickness 4 mm; n=1), T1-weighted TIRM (TI: 150.0 ms, TR: 20.0 ms, TE: 11.0 ms, slice thickness 3 mm; n=1), axial and coronal fast spin echo T2-weighted (TI: 150.0 ms, TR: 3000.0 ms, TE: 110.0 ms, slice thickness 3 mm; n=1), axial fat-suppressed 3D volume gradient echo T1-weighted images (TI: 80.0 ms, TR: 3.5 ms, TE: 1.1 ms, slice thickness 2 mm; n=1), axial contrast-enhanced T1-weighted images (TI: 5.0 ms, TR: 3.5 ms, TE: 1.1 ms, slice thickness 3 mm, n=1).

Intravenous contrast material (Gadovist, Schering AG, Berlin, Germany) was administered using a power injector (Medex, Medrad) into a cubital vein using a 16-gauge catheter. The dosage of contrast media was 0.025 mmol/kg at a rate of 3 ml/s, followed by a saline flush of 20 ml. Imaging was performed 1 min after intravenous injection of contrast material.

The exam was divided into three parts: pre-contrast imaging, dynamic imaging, late imaging. Pre-contrast imaging was performed using the TIRM technique. Dynamic imaging was performed using a T1-weighted SE sequence. The contrast-enhanced dynamic images were obtained with a 3D volume gradient echo sequence. Followed by arterial enhancement, the dynamic images were acquired in a sagittal plane to evaluate vascularization of the whole breast tissue. For this purpose, an additional sagittal T2-weighted sequence was acquired. The late imaging was divided into three steps: arterial enhancement, portal vein enhancement, and late arterial phase.

The imaging protocol was planned by the radiologist, who evaluated the results of all exams and decided if the suspicion of malignancy is confirmed. The decision was based on the evaluation of the number, size, and distribution of microcalcifications; if microcalcifications are associated with irregularities in breast tissue, if mass, if the enhancement of the mass is heterogeneous (isoechogenicity, hyperechogenicity, hypoechoic).

Histopathologic diagnosis

Histopathologic diagnosis of the excised lesion was obtained within 24 hours after the excision. The histological examination was performed on formalin-fixed and paraffin-embedded samples. The sections were stained with H&E and evaluated by the pathologist. The histological diagnosis was obtained using a standard H&E stain. The diagnosis was made using a standard diagnostic protocol.

The histological diagnosis was obtained by a pathologist with a minimum of 10 years of experience in diagnostic breast pathology. The pathologist was blinded to the imaging results. The diagnosis was based on the histological findings, including the type of lesion, the size of the lesion, the presence of microcalcifications, the presence of stromal hyperplasia, and the presence of any other pathological findings.

The pathologist evaluated the microcalcifications in the excised lesion and categorized them as benign or malignant. The pathologist also evaluated the microvasculature in the excised lesion and categorized it as normal or abnormal. The pathologist also evaluated the stromal hyperplasia in the excised lesion and categorized it as normal or abnormal. All of these findings were used to determine the final histological diagnosis.

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mm, 320 mm field of view [FoV]), sagittal T2-weighted fast spin echo with fat saturation (TR: 7300.0 ms, TE: 113.0 ms, slice thickness 4 mm, 180 mm FoV), axial T2-weighted turbo spin echo (TR: 4000.0 ms, slice thickness 4 mm, 380 mm FoV), axial T1-weighted three-dimensional (3D) gradient echo with fat saturation (TR: 4.3 ms, TE: 1.3 ms, slice thickness 0.8 mm, 340 mm FoV). Axial T1-weighted 3D gradient echo without fat saturation (TR: 16.0 ms, TE: 4.8 ms, slice thickness 2 mm, 320 mm FoV) before contrast administration and dynamic 3D axial T1-weighted gradient echo without fat saturation five times after the injection of the bolus of 0.1 mmol/kg of paramagnetic contrast agent (gadoterate meglumine, Dotarem ®) for both breasts were collected. Unenhanced images were then subtracted from the contrast-enhanced images on a pixel-by-pixel basis. Multiplanar reformating (MPR) reconstructions and maximum intensity projection (MIP) reconstructions were performed, with dynamic (kinetic) time-intensity curves generated in the selected region of interest (ROI).

CNB was performed after MRI, under US guidance, using a 14-gauge biopsy device (Monopty, Bard), with multiple passes per lesion. Mammography of the specimen was performed in order to confirm the presence of microcalcifications in the specimen. In patients with surgical excision of lesions, wire localization of microcalcifications was performed under US and correct position was confirmed by mammography. For sonographically invisible lesions, mammography guidance of biopsy, with a fenestrated compression paddle with alpha-numeric grid, was used.

Statistical analysis
Imaging findings were analyzed and reported using BI-RADS descriptors (10, 11). To calculate diagnostic accuracies of imaging methods, findings were dichotomized: negative examinations were defined as examinations with BI-RADS final assessment category of 1–3, while positive examinations were defined as examinations with final assessment category of 4 and 5. Positive predictive value (PPV3) was calculated as the number of detected cancers per positive examinations. The positive predictive value category 3 (PPV3) defined as per BI-RADS Atlas 5th edition is the rate of detected cancers (true positive) divided by all patients in whom biopsy was performed (true positive and false positive) (11). Since all our patients had biopsy performed after imaging work-up was finished, PPV3 was calculated in all cases. Sensitivity was calculated as the number of positive examinations for which there was a tissue diagnosis of cancer, divided by all cancers present in the study group. Specificity was calculated as the number of negative examinations for which there was no tissue diagnosis of cancer, divided by all examinations for which there was no tissue diagnosis of cancer. Negative predictive value (NPV) was calculated as the number of negative examinations for which there was no tissue diagnosis of cancer, divided by all negative examinations.

All clinical and imaging data were available to the reading radiologist, and findings were presented and discussed at the multidisciplinary breast team meetings. Mammographic and MRI examinations were interpreted by one of three co-authors (radiologists with 10–22 years of experience in breast imaging). Screening mammograms were evaluated by two radiologists independently and diagnostic mammograms by one. US exams and CNB were performed by a single examiner with 22 years of experience in breast imaging.

Data were analyzed using the Statistical Package for Social Sciences 16.0 (SPSS Inc.). Chi square, Fisher’s exact test and the Mann-Whitney U test were used for comparison of the groups, with two-tailed P value less than 0.05 considered statistically significant. Study sample size requirements were calculated based on a clinically acceptable degree of precision, at the estimated prevalence of disease in the target population, and at the hypothesized values of sensitivity, specificity, and predictive values; thus, at the estimated prevalence of the disease in the target population of 40% and at the hypothesized value of sensitivity equal to 85% the calculated required sample size was 123, and at the hypothesized value of specificity equal to 75% the calculated required sample size was 120, based on a 95% confidence interval of hypothesized sensitivity and specificity (33).

Results
Histologic diagnoses are presented in Table 1. Prevalence of malignancy in our study group was 38.4% (48/125). As shown in Table 1, pure DCIS comprised 52.1% of malignant cases, microinvasive lesions further 12.5%, and invasive lesions 35.4%. The details of other histopathologic findings can be found in Table 1.

<table>
<thead>
<tr>
<th>Histopathologic diagnoses of mammographic BI-RADS 4 and 5 microcalcifications in our study</th>
<th>No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant (n=48, 38.4%)</strong></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td>IDC</td>
<td>21 (43.8)</td>
</tr>
<tr>
<td>IDC+DCIS</td>
<td>7</td>
</tr>
<tr>
<td>DC mic</td>
<td>6</td>
</tr>
<tr>
<td>IDC</td>
<td>8</td>
</tr>
<tr>
<td>ILC</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>48 (100)</td>
</tr>
<tr>
<td><strong>Benign (n=77, 61.6%)</strong></td>
<td></td>
</tr>
<tr>
<td>Sclerosing adenosis</td>
<td>16 (20.8)</td>
</tr>
<tr>
<td>Flat epithelial atypia</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Complex sclerosing adenosis</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>LCIS</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>ADH</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Other benign changes- B2</td>
<td>43 (55.8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>77 (100)</td>
</tr>
</tbody>
</table>

DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; DC mic, microinvasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; ADH, atypical ductal hyperplasia.
Mammography as indicator for biopsy yielded PPV3 of 38.4%. Separately, mammographic BI-RADS 4 category yielded PPV3 of 34.5% (40/116 malignant microcalcifications), and BI-RADS 5 had PPV3 of 88.9% (8/9 malignant).

Results of US in workup of microcalcifications are shown in Tables 2 and 3. Sensitivity, specificity, PPV3, and NPV for US were: 85.4% (95% CI, 72.2–93.9), 66.2% (95% CI, 54.5–76.6), 61.2% (95% CI, 48.5–72.8), and 87.9% (95% CI, 76.7–95.0). Overall, 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% of cases) compared to benign ones (74%). However, difference in visibility between malignant and benign lesions did not reach statistical significance ($P = 0.18$). As summarized in Table 3, malignant and benign microcalcifications presented differently on US, with statistically significant difference. Finding “hyperechoic dots within hypoechoic mass, area or dilated ducts” was most commonly related to malignancy, with the highest PPV3 (67.3%). Isolated microcalcifications within normal breast tissue were seen only in benign cases, with NPV of 100%. High-risk lesions comprised a higher portion of false positive findings (44.4%, 8/18). Among false negative findings of US, 71.4% (5/7) were pure DCIS lesions, while the rest (28.6%, 2/7) were invasive lobular carcinoma.

Microcalcifications visible on US had larger mammographic diameter compared with those invisible on US, with statistically significant difference (median of mammographic size of cluster (mm), median (range): 29 (5–85) vs. 20 (6–58), $P = 0.037$).

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

<table>
<thead>
<tr>
<th>US visible n (%)</th>
<th>US invisible n (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant disease</td>
<td>41 (85.4)</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td>Benign disease</td>
<td>57 (74.0)</td>
<td>20 (26.0)</td>
</tr>
<tr>
<td>Total</td>
<td>98 (78.4)</td>
<td>27 (21.6)</td>
</tr>
<tr>
<td>Mammographic size of cluster (mm), median (range)</td>
<td>29 (5–85)</td>
<td>20 (6–58)</td>
</tr>
<tr>
<td>Mammographic BI-RADS category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI-RADS 4</td>
<td>89 (76.7)</td>
<td>27 (23.3)</td>
</tr>
<tr>
<td>BI-RADS 5</td>
<td>9 (100)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Table 3. US features of mammographic BI-RADS 4 and 5 microcalcifications

<table>
<thead>
<tr>
<th>US findings*</th>
<th>Malignant</th>
<th>Benign</th>
<th>Total (%)</th>
<th>PPV3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcalcifications within hypoechoic mass, area or dilated ducts</td>
<td>35</td>
<td>17</td>
<td>52 (41.6)</td>
<td>67.3%</td>
</tr>
<tr>
<td>Isolated microcalcifications</td>
<td>0</td>
<td>9</td>
<td>9 (7.2)</td>
<td>0</td>
</tr>
<tr>
<td>Heterogeneous regions without mass or clearly visible microcalcifications</td>
<td>6</td>
<td>31</td>
<td>37 (29.6)</td>
<td>16.2%</td>
</tr>
<tr>
<td>Negative (US invisible microcalcifications)</td>
<td>7</td>
<td>20</td>
<td>27 (21.6)</td>
<td>25.9%</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>77</td>
<td>125 (100)</td>
<td></td>
</tr>
<tr>
<td>US BI-RADS 1–3</td>
<td>7</td>
<td>51</td>
<td>58 (46.4)</td>
<td></td>
</tr>
<tr>
<td>US BI-RADS 4–5</td>
<td>41</td>
<td>26</td>
<td>67 (53.6)</td>
<td></td>
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</tbody>
</table>

*US findings of microcalcifications were significantly different between benign and malignant cases ($P < 0.001$).
mographic diameters: 29 mm vs. 20 mm; $P = 0.037$) (Table 2).

Detailed MRI features of microcalcifications are presented in Table 4. Sensitivity, specificity, PPV3, and NPV of MRI were 100% (95% CI, 92.6–100), 70.1% (95% CI, 58.6–80.0), 67.6% (95% CI, 55.5–78.2), and 100% (95% CI, 93.4–100). Overall, non-mass lesion enhancement was the most common presentation of microcalcifications (58.4% of all cases). We compared diagnostic accuracies separately for masses and non-mass lesions to test the influence of lesion type on diagnostic capabilities of MRI. There was no statistically significant association between lesion type and diagnostic accuracy ($P = 0.59$): sensitivity, specificity, PPV3, and NPV for masses were 100% (95% CI, 79.4–100), 50% (95% CI, 15.7–84.3), 80% (95% CI, 56.3–94.3), and 100% (95% CI, 39.8–100), and for non-mass lesions 100% (95% CI, 89.1–100), 53.7% (95% CI, 37.4–69.4), 62.6% (95% CI, 48.0–75.9), and 100% (95% CI, 84.6–100). However, masses had higher probability to be malignant (PPV3, 66.7%), compared with non-mass lesions (PPV3, 43.8%).

Figs. 1–3 show representative cases of conjoined mammography, US, and MRI workup of microcalcifications. Histologic diagnosis after second-look US-guided CNB was atypical ductal hyperplasia. Wide surgical excision was recommended because of highly suspicious findings of MRI. Diagnosis after excision was multiple foci of DCIS, and because of widespread area of non-mass enhancement seen on MRI, mastectomy was performed. Final diagnosis was microinvasive ductal carcinoma.

Discussion

In this study, consecutive enrollment of mammography, US, and MRI in the workup of microcalcifications resulted in MRI sensitivity, specificity, PPV3, and NPV of 100% (95% CI, 92.6–100), 70.1% (95% CI, 58.6–80.0), 67.6% (95% CI, 55.5–78.2), and 100% (95% CI, 93.4–100). Overall, non-mass lesion enhancement was the most common presentation of microcalcifications (58.4% of all cases). We compared diagnostic accuracies separately for masses and non-mass lesions to test the influence of lesion type on diagnostic capabilities of MRI. There was no statistically significant association between lesion type and diagnostic accuracy ($P = 0.59$): sensitivity, specificity, PPV3, and NPV for masses were 100% (95% CI, 79.4–100), 50% (95% CI, 15.7–84.3), 80% (95% CI, 56.3–94.3), and 100% (95% CI, 39.8–100), and for non-mass lesions 100% (95% CI, 89.1–100), 53.7% (95% CI, 37.4–69.4), 62.6% (95% CI, 48.0–75.9), and 100% (95% CI, 84.6–100). However, masses had higher probability to be malignant (PPV3, 66.7%), compared with non-mass lesions (PPV3, 43.8%).

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<table>
<thead>
<tr>
<th>MRI BI-RADS category</th>
<th>Malignant</th>
<th>Benign</th>
<th>Total (%)</th>
<th>PPV3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI BI-RADS 1</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
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<tr>
<td>MRI BI-RADS 2</td>
<td>0</td>
<td>21</td>
<td>21 (16.8)</td>
<td>0</td>
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<tr>
<td>MRI BI-RADS 3</td>
<td>0</td>
<td>33</td>
<td>33 (26.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MRI BI-RADS 4</td>
<td>8</td>
<td>21</td>
<td>29 (23.2)</td>
<td>27.6%</td>
<td></td>
</tr>
<tr>
<td>MRI BI-RADS 5</td>
<td>40</td>
<td>2</td>
<td>42 (33.6)</td>
<td>95.2%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>77</td>
<td>125 (100)</td>
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Table 4. MRI features of pure microcalcifications in correlation to histopathology

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<tr>
<th>MRI BI-RADS category</th>
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<th>Benign</th>
<th>Total (%)</th>
<th>PPV3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI BI-RADS 1</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MRI BI-RADS 2</td>
<td>0</td>
<td>21</td>
<td>21 (16.8)</td>
<td>0</td>
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</tr>
<tr>
<td>MRI BI-RADS 3</td>
<td>0</td>
<td>33</td>
<td>33 (26.4)</td>
<td>0</td>
<td></td>
</tr>
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<th>Benign</th>
<th>Total (%)</th>
<th>PPV3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI BI-RADS 1</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MRI BI-RADS 2</td>
<td>0</td>
<td>21</td>
<td>21 (16.8)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MRI BI-RADS 3</td>
<td>0</td>
<td>33</td>
<td>33 (26.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MRI BI-RADS 4</td>
<td>8</td>
<td>21</td>
<td>29 (23.2)</td>
<td>27.6%</td>
<td></td>
</tr>
<tr>
<td>MRI BI-RADS 5</td>
<td>40</td>
<td>2</td>
<td>42 (33.6)</td>
<td>95.2%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>77</td>
<td>125 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
in the literature, and vary from 23% to 97% (2, 5, 7, 12, 44, 45). But, we have found that, when microcalcifications are visualized with US, there is a statistically different presentation between malignant and benign microcalcifications. US finding of “hyperechoic dots within hypoechoic mass, area or dilated ducts” was most commonly related to malignancy, while finding of “isolated microcalcifications within normal breast tissue” was seen only in benign cases. Also, malignant microcalcifications in our study were more commonly visualized than benign (85.4% vs. 74%), which is in accordance with other studies (2, 14, 46). This permits us to presume that recognition of such different patterns of sonographic presentation of microcalcifications may add additional value when performing MRI after US, and thus improve MRI performance for microcalcifications.

Regarding different MRI BI-RADS imaging features, we noticed that lesion type (mass vs. non-mass) did not influence significantly on the diagnostic accuracy of MRI, with similar sensitivity and specificity for both subgroups, which is opposite to the findings so far published in the literature. To our knowledge, there are only two previous studies which analyzed individual MRI BI-RADS descriptors associated with malignancy in cases of microcalcifications, and our results are in agreement with earlier published data (31, 41). However, no prior study assessed PPVs of different MRI features in the workup of microcalcifications. As shown in Table 4, MRI morphologic features of masses with highest PPV3 in our study were irregular shape, spiculated margin, and heterogeneous internal enhancement. For the non-mass enhancement lesions, malignancy was typically represented by segmental distribution and clumped internal enhancement. Wash-out kinetic dynamic enhancement curve was highly indicative of malignancy, both for masses and non-mass lesions.

We analyzed earlier reports on diagnostic performances of MRI in workup of microcalcifications (3, 4, 31, 34–43). Those reports vary substantially in methodology and results, with sensitivities ranging from 45% to 100%, and specificities from 51% to 100%. Recently, a review and meta-analysis study was published by Bennani-Baiti and Baltzer (15), aiming to clarify the role of MRI in assessment of mammographic BI-RADS 3–5 microcalcifications. Twenty studies met their inclusion criteria, with 1843 lesions and a mean prevalence of malignancy of 40.6%. It is interesting that seven of those 20 studies were published after 2014, while the oldest study dated from 1996. Authors revealed pooled sensitivity and specificity of 92% and 66% for BI-RADS 4 lesions, 57% and 32% for BI-RADS 3 lesions. Their conclusion was that MRI is not recommended for diagnosis of malignancy in BI-RADS 3 and 5 mammographic microcalcifications but can be considered for BI-RADS 4 microcalcifications.

We analyzed potential biases which might have influenced our results. As shown in our study, pure microcalcifications present most commonly as non-mass lesions (Table 4). Non-mass lesions are well recognized as the problem makers in breast MRI: most readers have problems in the interpretation of non-mass lesions, while inexperienced readers’ ability to differentiate benign from malignant non-mass lesion can be close to guessing (6). This points out importance of experience in cases of microcalcifications. In our study only experienced readers were included, but we did not perform interobb-
Also, mammography of biopsy specimens 
experience in breast imaging, including US). 
form all US-guided CNB (22 years of expe 
single highly experienced radiologist per 
but tried to address this issue by having a 
croc calcifications. We used US-guided CNB 
First, vacuum-assisted biopsy is considered 
DCIS on sensitivity of MRI in our study. 
we did not have false negative MRI find 
study (71.4%). But, as mentioned earlier, 
was excluded, the pooled negative pre 
er
server variability analysis, which prevents 
us from drawing a conclusion about the 
influence of readers’ experience on re 
results. Next potential bias is patient sele 
tion procedure. There are some reports 
that performances of MRI in microcalcifi 
cations are somewhat better for invasive 
lesions (15). Prevalence of malignancy in 
our study was 38.4%, which is close to av 
average published rates (around 40%), and 
declines one of the possible patient se 
lection biases. Prevalence of DCIS among 
malignant lesions is also recognized as a 
potential cause of lower specificity of MRI 
in microcalcifications. In the review study 
published by Bennani-Baiti and Baltz 
er (15), among 1843 lesions, there were 
106 false-negative findings (5.8%), 68 of 
which (64.2%) were DCIS only. When DCIS 
was excluded, the pooled negative pre 
dictive value of breast MRI to rule out in 
avasive or microinvasive cancer was found 
to be significantly higher, reaching 99%. 
DCIS comprised 52.1% of our malignant 
cases (Table 1) and was the major cause 
of false negative findings of US in our 
study (71.4%). But, as mentioned earlier, 
we did not have false negative MRI find 
ings, so we cannot assess the influence of 
DCIS on sensitivity of MRI in our study. 
There are several limitations to our study. 
First, vacuum-assisted biopsy is consid 
ered the method of choice in cases of pure 
microcalcifications. We used US-guided CNB 
due to organization of work in our facility 
but tried to address this issue by having a 
single highly experienced radiologist per 
form all US-guided CNB (22 years of expe 
rience in breast imaging, including US). 
Also, mammography of biopsy specimens 
was performed to confirm the presence 
of microcalcifications. Second, we did not 
perform interobserver variability tests for 
MRI results, which leaves us without 
quantitative analysis of the exact effect of 
experience on diagnostic accuracy of a 
method. Also, we did not perform blinded 
MRI reading (without knowledge of prior 
US findings). Therefore, we cannot com 
pare blinded and non-blinded results, and 
thus cannot assess exact influence of per 
forming US prior to MRI on final results of 
MRI. We can just assess combined methods 
diagnostic accuracy (US + MRI), presented 
through diagnostic accuracy achieved with 
MRI. We did not perform detailed analysis 
on different subgroups of cases (such as US 
or MRI features for different histologic diag 
noses, for different type of microcalcifica 
tions according to mammographic BI-RADS 
descriptors, for breast density, patients, he 
reditary risk for breast carcinoma, correla 
tion of microcalcifications area diameter to 
MRI findings), which prevents us from ana 
alyzing the influence of those covariates on 
our results. Finally, we did not analyze the 
number of false positive findings found on 
MRI in the contralateral breast or in other 
parts of the same breast. 
In conclusion, the aim of our study was 
to test the suitability of conjoined use of 
mammography, US, and MRI in the evalu 
ation of mammographic BI-RADS 4 and 5 
microcalcifications. In such settings, MRI 
reaches NPV of 100%, which supports the 
application of MRI for exclusion of malig 
nancy, and suggests that negative MRI may 
influence the decision to biopsy microcalcifi 
cations. However, further work with larg 
er number of cases is needed to validate 
our results. There is statistically significant 
difference in presentation between malig 
nant and benign microcalcifications when 
MRI BI-RADS descriptors are applied in the 
analysis. Microcalcifications appear most 
commonly as non-mass lesions, which is 
important to keep in mind when MRI is 
used for the workup of microcalcifications, 
since non-mass lesions are the major cause 
of possible false negative findings of MRI. 
On the other hand, US cannot reliably ex 
clude malignancy nor decline the need for 
biopsy. However, when microcalcifications 
are visualized with US prior to MRI, recog 
nition of a different pattern of sonographic 
presentation of malignant and benign mi 
icrocalcifications may add additional value 
to the performance of MRI.

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Conflict of interest disclosure 
The authors declared no conflicts of interest.

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