Abstract. Aim: To retrospectively evaluate the diagnostic value of high-frequency ultrasound for the detection of microcalcifications screening in BI-RADS 4a patients. Patients and Methods: A total of 52 women (mean age 60.5±6.5 years) classified as BI-RADS 4a with microcalcifications, but without associated masses after X-ray mammography (XRM) underwent ultrasound (US) examination (B-mode, ApliPure™, and MicroPure™ imaging). The results were assessed by two independent investigators and analyzed in relation to the B-classification. Written informed consent was obtained before enrolment. Results: The rate of US microcalcification detection was 98.1% (B-mode), 100% (ApliPure™) and 25% (MicroPure™), respectively. The microcalcification extent was significantly underestimated with all US modalities in comparison with XRM, but the difference was lower for ApliPure™ as compared to B-mode. ApliPure™ was also superior in terms of puncture feasibility, facilitating US-guided biopsy in 67.3% as compared to 48.1% (B-mode) and 15.4% (MicroPure™). Conclusion: In BI-RADS 4a patients, both high-frequency B-mode US and ApliPure™ imaging are highly sensitive for the detection of microcalcifications, whereas MicroPure™ ultrasound imaging is unsuitable. ApliPure™ imaging allowed US guided biopsy for 67.3% of lesions, providing a convenient and economical alternative to stereotactically guided biopsy.

Microcalcifications detected by screening X-ray mammograms (XRM) have a positive correlation with breast cancer (1); indeed, they may be the only evidence of early stage, non-palpable breast cancer (2). Thus, the detection of microcalcifications is of crucial importance for the diagnosis and treatment of early breast cancer (3), one of the few cancer types that can be treated with hope for a cure (4, 5).

The detection of microcalcifications facilitates the diagnosis of about 50% of occult breast malignancies (6). Although about 25% (7) of patients with calcifications suffer from breast cancer, the specificity of mammographically visible microcalcifications for the detection of breast cancer lesions is low, and benign calcifications can often not be sufficiently distinguished from those indicating malignancy (7-10). To triage patients with mammary microcalcifications and other abnormalities in a standardized manner in screening XRMIs, the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) (11) has established the BI-RADS system; recently, the category BI-RADS 4 (‘suspicious abnormality’ (11)) has been divided into three subgroups (BI-RADS 4a, 4b, and 4c) according to the risk of malignancy (approximately 2% in group 4a as opposed to 95% in group 4c (12)). Despite the low risk in BI-RADS 4a lesions, biopsy is mandatory in order to detect possible malignancies (which would, moreover, most likely be operable).

Breast biopsies can be performed in various ways: stereotactically by XRM guidance, by magnetic resonance tomography guidance, by US guidance, or using an open surgical procedure. Recently, advances in US technology...
have enabled radiologists to provide efficient US guidance for percutaneous biopsies: this is considered to be an inexpensive, fast and simple way to collect histopathological specimens (13, 14). To perform US-guided breast biopsies, a close sonographic determination of the target is a self-evident prerequisite. Therefore, either the tumor or the tumor-associated microcalcifications have to be detectable by means of US.

In the past, the usefulness of US for the detection of mammary microcalcifications was debated in the literature (15-19). On the one hand, authors claimed high sensitivities and specificities of up to 95% and 88%, respectively (19), while other authors concluded that US was unsuited for this purpose (15). To date, no imaging modality other than XRM has achieved an accepted role in the detection of mammary microcalcifications (20, 21). Since the implementation and improvement of high-frequency US equipment, however, the quality of breast US has improved markedly (21). Technology has developed to a point today where it can be assumed that a commercially available, state-of-the-art, high-frequency US system working with a 13 megahertz (MHz) transducer may be able to reliably detect microcalcifications associated with mammary abnormalities that are in all probability malignant.

The aim of this retrospective study was to determine the diagnostic value of the Aplio XG V3™ US system (Toshiba Medical Systems GmbH, Neuss, Germany) for the detection of mammary microcalcifications and associated breast masses in patients classified as ACR BI-RADS 4a. We therefore determined: a: the sensitivity for the detection of mammary microcalcifications using the above US system in three different settings; b: the visibility of breast microcalcifications according to a qualitative score; c: the feasibility of an US-guided biopsy with these US settings. The US settings were statistically compared to XRM and between each other for the aforementioned values.

<table>
<thead>
<tr>
<th>Histopathologic finding</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blunt duct adenosis with/without other benign non-mass lesions</td>
<td>28</td>
<td>53.8</td>
</tr>
<tr>
<td>Other benign non-mass lesions without blunt duct adenosis</td>
<td>10</td>
<td>19.2</td>
</tr>
<tr>
<td>Fibroadenoma with/without associated benign non-mass lesions</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Other benign mass lesions</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>DCIS</td>
<td>7</td>
<td>13.5</td>
</tr>
<tr>
<td>DCIS + invasive breast cancer</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
</tr>
</tbody>
</table>

DCIS: Ductal carcinoma in situ.

Table II. Size of the microcalcifications. All ultrasound settings underestimated the size of the microcalcifications (p<0.001).

<table>
<thead>
<tr>
<th>Ultrasound</th>
<th>Mean size (mm)</th>
<th>Minimum size (mm)</th>
<th>Maximum size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRM</td>
<td>30.0±21.8</td>
<td>8</td>
<td>105</td>
</tr>
<tr>
<td>B-mode</td>
<td>5.9±2.7</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>ApliPure™</td>
<td>7.6±3.2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>MicroPure™</td>
<td>4.4±3.3</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

Patients and Methods

Patients/Screening program. A total of 52 consecutive patients [50.4-70.0 (mean 60.5±6.5) years of age] who attended a certified breast screening facility (Diavero Diagnosezentrum, Essen, Germany) within the framework of the German mammography screening program between May and October 2008 and fulfilled the inclusion criteria voluntary participation in the breast cancer screening program; no history of previous breast cancer; X-ray screening mammography findings rated as BI-RADS 4a; the presence of visible microcalcifications; no associated breast masses; and available histopathology as a reference standard) were included in this retrospective analysis. A written patient history and an XRM of both breasts were obtained, and images were evaluated by two independent breast radiologists 7 days after the examination. All patients enrolled in the present study were classified as BI-RADS 4a and hence were referred for further evaluation by breast sonography and stereotactic biopsy.

Screening mammography. All full-field digital XMRs (FFDM) were performed with a Novation™ mammography system (Siemens Medical Solutions, Erlangen, Germany). Standardized cranio-caudal and medio-lateral oblique images of both breasts were obtained, assessed by two independent investigators and stored digitally in the Picture Archiving and Communication System (PACS, JiveX™; VISUS Technology Transfer GmbH, Bochum, Germany).
Parameters for evaluation were chosen in accordance with (10): overall breast composition: fatty, heterogeneous, dense; visibility of microcalcifications according to the parameters described in the literature (10, 17, 18); extent of the microcalcification, defined as the greatest distance between two microcalcification points, in millimetres, measured with the PACS’ distance measuring function; distribution of microcalcification: clustered, linear, segmental; shape of microcalcification: round, punctuate, amorphous, heterogeneous, linear branching; visibility of associated breast masses (dichotomic: yes or no).

Breast US. All patients underwent breast sonography 5 to 50 days (mean, 11.6±5.8 days) after mammography. The system (Aplio XG V3™ US system, Toshiba Medical Systems GmbH, Neuss, Germany) was equipped with two special imaging modes (ApliPure™ and MicroPure™) in addition to the ‘conventional’ B-mode. ApliPure™ is a real-time compound imaging modality that performs spatial compounding and frequency compounding simultaneously, creating a smooth image impression, a low number of moving artefacts and a high lateral resolution (Figure 1). MicroPure™ is based on the visualization of hyperechoic microcalcifications beyond a specific threshold. A color filter highlighting microcalcifications in purple can be superimposed on the B-mode image (Figure 1).

For US investigation, the patients were positioned. If necessary, the patient was moved into a contralateral posterior oblique position to scan the lateral and inferior parts of the breast. Ultrasound was performed in supine position with raised arms in radial, antiradial, and...
longitudinal and transverse directions (10, 22) on the basis of the X-ray mammogram findings. The mean examination time was 7.0±3.6 min (range, 5-19 min). All US examinations were performed by a radiologist specialized in breast radiology with more than 15 years' experience in breast sonography. The investigations were performed in the presence of a gynecological consultant. The images were stored digitally in the Digital Imaging and Communications in Medicine (DICOM) format and evaluated by the same two radiologists who had evaluated the conventional XRM. Still images of either modality were evaluated in one session; images were not labeled according to the mode, but B-mode, ApliPure™ and MicroPure™ are clearly discernible by an experienced radiologist.

The evaluation of the B-mode images was performed by the same radiologists who evaluated the XRM in a modification of the aforementioned study (10) using the following parameters: quality of the microcalcification visibility on a 4-point scale: well visible, fairly visible, poorly visible, not visible; extent of the visible microcalcification, defined as the greatest distance between two microcalcification points (mm), measured with the distance measuring function of the US system; visibility of associated breast masses (dichotomic: yes or no); estimated feasibility of US-guided biopsy according to a 3-point scale: quite feasible; difficult, but feasible; not feasible (based on the possibility of identifying microcalcifications/associated masses in the surrounding tissue, the size of the lesion and its depth below the mammarian surface).

**Standard of reference.** XRM served as the standard of reference for the detection of microcalcifications by sonography. Histopathology served as the standard of reference for the detection of microcalcification-associated breast masses. All patients underwent stereotactic, vacuum-assisted biopsy using an ATEC™ system (Suros Surgical Systems, IN, USA) working with a 9-gauge needle 1-5 days (mean, 1.1±0.6 days) after US examination. All histopathological specimens were evaluated by two pathologists specialized in gynecological pathology (firstly, by a pathologist working as a private practitioner; secondly, by a gynecological pathologist from the breast cancer reference center at the University Hospital Münster, Münster, Germany). Diagnoses were made in consensus.

**Statistical analysis.** Data was analyzed according to the Standards for Reporting of Diagnostic Accuracy recommendations (23). The following descriptive and comparative statistical analyses were performed (software package SPSS for Windows, V. 14.5): sensitivity of the detection of microcalcifications by the three US modalities; differences in the extent of the microcalcifications between XRM and the various US settings (Mann-Whitney U-test); comparison of the microcalcification visibility and the feasibility of performing US-guided biopsies for the different US settings (Chi-square test); odds ratios with 95% confidence intervals (CI) for measuring function of the US system; visibility of associated breast masses; feasibility; not feasible (based on the possibility of identifying microcalcifications/associated masses in the surrounding tissue, the size of the lesion and its depth below the mammarian surface).

**Results**

**Histopathology.** Microcalcifications detected by XRM were histopathologically verified in all patients. According to the B-Classification of the Guidelines for Non-operative Diagnostic Procedures and Reporting in Breast Cancer Screening (24), 36 (69.2%) patients were assigned to group B2 (‘benign’), 6 (11.5%) patients to group B3 (‘benign, but of unknown biological potential’), no patient to group 4 (‘suspicious’), 7 (13.5%) patients to group B5a (‘malignant, in situ’) and 3 patients (5.8%) to B5b (‘malignant, invasive’).

In 20 patients (41.9%) associated breast masses that had eluded XRM were histopathologically confirmed. In 3 patients (5.8%) invasive breast tumors were detected, and in 2 out of these 3 patients (3.8%) invasive cancer was accompanied by a ductal carcinoma in situ (DCIS). In 7 additional patients (13.5%), a DCIS was detected without any additional invasive tumor. The remaining 32 patients (61.5%) had benign changes without associated masses in histopathological work-up, e.g. blunt-duct adenoses or inflammatory changes. For a detailed overview of the histopathological results, see Table I.

**X-ray mammography.** On XRM, 21 patients’ breasts (40.4%) were rated as dense and 31 as heterogeneous (59.6%). No breasts were rated as fatty. The mean expanse of the mammary microcalcifications was 30.0±21.8 mm (range, 8-105 mm; Table II). Concerning the distribution of the microcalcifications, in 28 cases (53.8%) they were classified as clustered, in 1 case (1.9%) as linear, and in 23 cases (44.2%) as segmental. The shape of the microcalcifications was amorphous in 27 cases (51.9%), heterogeneous in 14 patients (26.9%), linear branching in 6 patients (11.5%), and punctate in 5 patients (9.6%); no shape was rated as round. The extent of the microcalcifications (B2: 30.0±19.1 mm, B3: 32.8±36.7 mm, B5a: 23.9±20.9 mm, B5b: 37.7±27.7 mm), as well as the distribution of shapes, had no appreciable relationship to the histopathological B-classification.

**B-mode US.** The sensitivity of B-mode US imaging for the detection of microcalcifications was 98.8% (51/52 patients) (Figure 2). The quality of the microcalcification visibility was rated as ‘good’ in 29 patients (55.8%), ‘fair’ in 15 patients (28.8%) and ‘poor’ in 7 patients (13.5%) (Table III). The mean extent of the detected intramammary microcalcifications (n=51) was 5.9±2.7 mm (range, 2-14 mm) and therefore significantly smaller than that detected by XRM (p<0.0001).

The only microcalcified lesion eluding B-mode sonography was an invasive carcinoma (B5b). Neither visibility nor extent of microcalcifications in B-mode were related to the B-classification.

The technical difficulty of performing an US-guided biopsy was estimated as ‘quite feasible’ in 10 patients (19.2%), ‘difficult, but feasible’ in 15 patients (28.8%), and ‘not feasible’ in 27 patients (51.9%) (Table IV). Feasibility was significantly more likely in malignant lesions; whereas biopsy was rated ‘feasible’ in 8 out of 10 lesions with malignancy (80.0%), the same was true in only 17 out of 42 benign lesions [40.5%, odds ratio 5.88 (95% CI 1.24-27.99), p=0.02].
ApliPure™ US. The sensitivity of ApliPure™ US imaging for the detection of microcalcifications was 100% (52/52 patients). The quality of the microcalcification visibility was rated as ‘good’ in 41 patients (78.8%, Figure 2), ‘fair’ in 8 patients (15.4%) and ‘poor’ in 3 patients (5.8%). Hence, ApliPure™ US was slightly, but not significantly more sensitive for the detection of microcalcifications than B-mode ($p=0.0799$).

The mean extent of the microcalcifications was 7.6±3.2 mm (range, 2-16 mm) and thus also significantly smaller than that detected by XRM ($p<0.0001$), but significantly larger than that detected in B-mode US ($p<0.0001$).

Visibility and extent of microcalcifications were not related to B-classification.

The possibility of performing an US-guided biopsy was judged as ‘quite feasible’ in 18 patients (34.6%), ‘difficult, but feasible’ in 17 patients (32.7%), and ‘not feasible’ also in 17 patients (32.7%); the feasibility was not significantly related to malignancy [odds ratio 2.22 (95%-CI 0.42-11.69)].

MicroPure™ US. MicroPure™ US imaging detected microcalcifications in only 13 out of the 52 patients, rendering the method inadequate for this purpose (Figure 3). The possibility of performing an US-guided biopsy was judged as ‘quite feasible’ in 6 patients (11.5%), ‘difficult, but feasible’ in 2 patients (3.8%), and ‘not feasible’ in 44 patients (84.6%); MicroPure™ was therefore basically also unsuitable for biopsy.

All in all, ApliPure™ US was rated as the best US setting for US-guided breast biopsy, B-mode as the second best, and MicroPure™ as the third (ApliPure™ versus B-mode: $p=0.096$; ApliPure™ versus MicroPure™: $p<0.0001$; B-mode versus MicroPure™: $p<0.0001$).

### Discussion

Microcalcifications consist of small crystals of calcium apatites, which arise from several mechanisms in the human body (25). Their detection is the key to early breast cancer diagnosis and treatment, as 60-80% of all breast cancer lesions contain microcalcifications (26). Our study demonstrates that the detection of mammary microcalcifications by high-frequency US (conventional B-mode and ApliPure™ mode) is as reliable as that of XRM. The MicroPure™ mode, although primarily developed for the detection of mammary microcalcifications, failed to demonstrate them in the majority of patients; it also failed to facilitate biopsy in most lesions, rendering the method unsuitable at the moment.

Despite its high sensitivity, US – regardless of which mode was used – significantly underestimated the size of the microcalcifications, the difference being lowest in ApliPure™. The latter was also the most appropriate mode for US-guided breast biopsies, which was feasible for nearly two thirds of the lesions.

The high sensitivity of the B-mode imaging for the detection of microcalcifications found in our study confirms, and indeed exceeds, previously published findings (19, 27, 28); other authors, however, found US to be a less suitable method for this purpose, reporting a sensitivity of only about 60% for B-mode Ultrasound (10, 15). Thus, the higher sensitivity in the present study is probably attributable to technical advancement in US equipment, and notably the ApliPure™ real-time compound imaging modality that facilitates image evaluation due to smoothing of the image and the low number of moving artifacts.

In former studies as predictive factors for the detectability of microcalcifications by US a clustered arrangement, a large number of particles, as well as a BI-RADS 5 category were described. With the use of state-of-the-art US techniques, therefore, a substantial limitation seems to have been overcome. With conventional B-mode imaging, as well as with ApliPure™ imaging, almost all microcalcifications in

### Table III. Sensitivity of different ultrasound settings for the detection of microcalcifications/qualitative visibility of microcalcification according to a 4-point score (well visible/fairly visible/poorly visible/not visible). ApliPure™ ultrasound was rated as the best ultrasound setting for the detection of microcalcifications, B-mode as the second best, MicroPure™ as the third (ApliPure™ versus B-mode: $p=0.0095$; ApliPure™ versus MicroPure™: $p<0.0001$; B-mode versus MicroPure™: $p<0.0001$).

<table>
<thead>
<tr>
<th></th>
<th>B-mode</th>
<th>ApliPure™</th>
<th>MicroPure™</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>52</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>%</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>51/52</td>
<td>100.0</td>
<td>13/52</td>
</tr>
<tr>
<td>Good visibility</td>
<td>29</td>
<td>55.8</td>
<td>41</td>
</tr>
<tr>
<td>Fair visibility</td>
<td>15</td>
<td>28.8</td>
<td>8</td>
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<tr>
<td>Poor visibility</td>
<td>7</td>
<td>13.5</td>
<td>3</td>
</tr>
<tr>
<td>Not visible</td>
<td>1</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
<td>52</td>
</tr>
</tbody>
</table>

### Table IV. Feasibility of ultrasound-guided breast biopsy of suspicious areas using different ultrasound settings. ApliPure™ ultrasound was rated as the best ultrasound setting for ultrasound-guided breast biopsy, B-mode as the second-best, MicroPure™ as third (ApliPure™ versus B-mode: $p=0.0011$, ApliPure™ versus MicroPure™: $p<0.0001$, B-mode versus MicroPure™: $p<0.0001$).

<table>
<thead>
<tr>
<th></th>
<th>B-mode</th>
<th>ApliPure™</th>
<th>MicroPure™</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>52</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>%</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Quite feasible</td>
<td>10</td>
<td>19.2</td>
<td>18</td>
</tr>
<tr>
<td>Difficult, but feasible</td>
<td>15</td>
<td>28.8</td>
<td>17</td>
</tr>
<tr>
<td>Not feasible</td>
<td>27</td>
<td>51.9</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>100.0</td>
<td>52</td>
</tr>
</tbody>
</table>
BI-RADS 4a lesions were detectable, regardless of their size and distribution and the B-classification of the lesions.

This obviously only applies to calcifications of similar dimensions. All US modalities significantly underestimated the extent, probably due to the two-dimensional imaging as opposed to the projection of three dimensions in XRM (19). Since the best US mode (ApliPure™) underestimated the extent by about 20 mm, this may be speculated as a detection threshold for US at the moment.

Another considerable issue that may explain discrepancies between studies is the well-known examiner dependency of US diagnostics and the fact that the examiner, in this case highly experienced, knew that microcalcifications had been detected in XRM. However, this situation reflects exactly the procedure in breast cancer screening programs, rendering the results all the more relevant.

The explanation for the relatively low detectability of microcalcifications by the MicroPure™ mode is due to the software algorithm, especially the filtration of hyperechoic signals. MicroPure™ imaging will therefore probably provide a high specificity in the detection of mammary microcalcifications, which is however irrelevant in the present study, and the clinical screening setting.

The reliable US detection and biopsy of microcalcifications has a number of ostensive advantages: Ultrasound-guided biopsies are less expensive than stereotactic biopsies, and they can be performed without stereotactic equipment (10, 14, 29-31). Patients prefer US-guided biopsies because they feel more comfortable without breast compression (18, 32); faster biopsy performance, real-time control and the lack of ionizing radiation are additional advantages of this method (18, 32, 33). However, the present results only apply to patients with a low suspicion of malignancy (BI-RADS 4a); additional studies are needed to confirm the findings for other BI-RADS groups. Another issue to be considered is the relatively high percentage of malignancies in the present trial (22.1%) as compared to published series (e.g. 17% of 225 patients in all BI-RADS 4 categories (34)).

A limitation of our study is that the feasibility of biopsy was assessed without actually performing it. Previously published studies, however, suggest that breast US is an effective alternative to stereotactic guidance (13, 31, 35-37).

Unlike Soo and coworkers (17), we found no association between microcalcification detectability and lesion class. Whereas malignant lesions provide a hypoechoic background that facilitates the detection of associated microcalcifications (19, 38), this is obviously not a necessary prerequisite.

**Conclusion**

In BI-RADS 4a patients, B-mode and ApliPure™, but not MicroPure™, US imaging were highly sensitive for the detection of microcalcifications. Ultrasound significantly underestimated the size of the microcalcifications. ApliPure™ also allowed US guided biopsy for the majority of lesions, rendering it the most suitable among the three modes under investigation. As a consequence, US-guided biopsy of areas with microcalcifications and/or associated breast masses seems to be feasible, and this may facilitate and accelerate breast biopsies, as well as make them more economical and comfortable in comparison with stereotactic biopsies.

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**References**


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