Management of Breast Lesions Detectable Only on MRI
Abklärung ausschließlich MRT-detektierbarer Mammaläsionen

Key words
- breast
- MR imaging
- interventional MRI

Abstract
Breast MR imaging has become established as the most sensitive imaging method for diagnosing breast cancer. As a result of the increasing examination volume and improved image quality, the number of breast lesions detected only on MRI and requiring further clarification has risen in recent years. According to the S3-guideline “Diagnosis, Therapy, and Follow-Up of Breast Cancer” as revised in July 2012, institutions performing breast MRI should provide the option of an MRI-guided intervention for clarification. This review describes the indications, methods and results of MRI-guided interventions for the clarification of breast lesions only visible on MRI. Recent guidelines and study results are also addressed and alternative methods and pitfalls are presented.

Key points:
- Up to 57% of lesions originally visible only on MRI can be sonographically correlated and biopsied.
- MRI-guided intervention is necessary for the clarification of BI-RADS® 4 and 5 lesions detectable only on MRI
- MRI-guided vacuum-assisted breast biopsy should be preferentially used
- MRI-guided localization and surgical excision should be used if MRI-guided vacuum-assisted biopsy is not possible
- If BI-RADS® 4 and 5 findings visible only on MRI are not detectable on interventional MRI, a follow-up MRI should be performed within six months

Introduction
Dynamic contrast-enhanced magnetic resonance mammography (MRM) has become established as the most sensitive imaging method in the field of senology [1, 2]. As a result of the increasing examination volume and improved image quality, the number of MRI-detected breast lesions requiring further clarification has risen in recent years. In the 1990s, MRI-guided marking with subsequent excision biopsy and MRI-guided core biopsy were developed as alternative procedures. First described in 1999, vacuum-assisted biopsy (VAB) [3] represents a technical advancement and, in its current form, is the method of choice. The latest German S3-guideline “Diagnosis, Therapy, and Follow-Up of Breast Cancer” as revised in July 2012, recommends that institutions performing breast MRI should provide the option of an MRI-guided intervention for clarification.
of Breast Cancer” accordingly mandates that MRI-VAB is to be used for the histological confirmation of lesions that are visible only on MRI [4]. This is in line with the recommendations of an interdisciplinary European consensus paper [5]. The S3-guideline as updated in July 2012 recommends performing MRM only if there is the possibility of performing an MRI-guided intervention [4]. Although external partners can be consulted, many institutions are now faced with the challenge of learning how to perform MRI-guided breast interventions. The goal of this review is to present all aspects essential for clarifying breast lesions detectable only on MRI.

**Indication for MRI-guided breast intervention**

MRM findings are described and categorized according to the Breast Imaging Reporting and Data System (BI-RADS®) [6]. Using a score system or catalog of features can aid classification [7–9]. Suspicious (BI-RADS® 4) and suggestive (BI-RADS® 5) findings must be verified histologically. If these findings are undetectable via mammography and ultrasound, MRI-guided intervention is necessary (Fig. 1). If MRI-assisted biopsy cannot be performed for technical or patient-related reasons, MRI-guided lesion marking with subsequent surgical excision biopsy represents an alternative. In certain cases (e.g. known cancerous lesion in the same quadrant of the breast), primary MRI-guided marking of lesions detectable only on MRI can be helpful.

**Mammographic and sonographic correlation (“second look”)**

Once a patient is diagnosed with a suspicious breast lesion (BI-RADS® 4 or 5) that is visible only on MRI, the mammograms should first be re-examined and a targeted ultrasound examination (“second look”) should be performed. If originally obscured findings are visible on mammography or ultrasound (Fig. 2), ultrasound- or mammography-guided biopsy should be performed [4, 5]. To ensure optimal ultrasound detection, the examination should be performed by a person possessing a high level of breast ultrasound expertise [10]. In any case, the MRM image data should be available during the ultrasound examination in order to ensure the best possible correlation in terms of the morphology, size and location of the findings. Additionally, a high-resolution linear transducer (ideally ≥ 12 MHz) can be helpful to localize even small findings with certainty. In fact, up to 57% of lesions originally visible only on MRI can be sonographically correlated and biopsied when a transducer of at least 12 MHz is used [10–12]. A positive correlation is present if the ultrasound finding matches the contrast-enhanced lesion detected by MRI in terms of location in the breast, shape and size [10]. Otherwise, MRI-guided clarification is advised [11]. In the case of a benign ultrasound-guided biopsy of the MRI finding and a clear ultrasound correlate, a follow-up examination is recommended if there is a concordant pathological-radiological correlation [4, 5]. Per the S3-guideline, a histopathologically benign biopsy of a lesion classified as BI-RADS® 4 or 5 warrants one-time follow-up imaging after a period of 6 to 24 months.
12 months [4]. Because lesions that are suspicious on MRI but lack a correlate in “second-look” ultrasound are malignant in 13 – 22% of cases [11 – 13], these should also be histologically verified via MRI-guided intervention.

**Technical aspects**

In principle, the same technical and equipment-related prerequisites as for diagnostic MRM apply to MRI-guided breast interventions [14 – 16]: field strength of at least 1.5 Tesla, surface coils, dynamic T1-weighted (T1-w) 2D or preferably 3D gradient echo (GE) sequence with the highest possible spatial resolution at a temporal resolution of 60 – 120 seconds per series, preferably transverse slice orientation, automated IV contrast medium injection (0.1 – 0.2 mmol gadolinium chelates per kg of body weight) with a flow rate of 3 milliliters (ml) per second and subsequent bolus injection of 20 ml physiological saline solution (0.9 % NaCl). For reliable lesion imaging, subtraction series of every contrast-enhanced series should be acquired.

The patient is in a prone position during the examination. The procedure of performing MRI-guided breast intervention in a supine position as developed in the 1990s [17] is no longer used because of its disadvantages (above all limited breast fixation capability and unfavorable ventrodorsal access). In addition to the surface coil, a targeting system and an apparatus for breast fixation must be present. Dedicated multi-channel breast biopsy coils – currently available from any MRI equipment manufacturer – should preferably be used. These allow breast compression along the mediolateral axis. As targeting systems, post-pillars or grids can be mounted medially or laterally (Fig. 3). In principle, the shortest possible access should be selected, the medial access being more difficult due to the longer distance in conjunction with the reduced light and operating space beneath the patient. At our center we therefore use medial access only if the distance from the lesion to the medial skin is less than 10 mm and safe lateral access is not possible. If lateral access is selected for medically located findings, post-biopsy clip insertion or, in the case of MRI-guided marking, clip or coil insertion (no wire) is recommended to ensure short intramammary wire routing through subsequent ultrasound- or mammography-assisted wire marking of the clip or coil. Alternatively to biopsy coils, perforated plate systems can be used together with flexible ring coils placed around the breast. In our experience, perforated plate systems are sometimes advantageous for reaching findings close to the thoracic wall. Compared to multi-channel breast biopsy coils, however, a ring coil is associated with a reduced signal-to-noise ratio and thus inferior image quality. This is true particularly for findings far from the coil (close to the nipple).

All targeting systems are equipped with MRI-visible markers, known as fiducial markers, which serve as references for determining lesion coordinates. These coordinates can be ascertained either manually by reading out the slice coordinates and depth measurements on the MRI console or automatically by means of special targeting software. The lesion coordinates ultimately have to be transferred manually to the targeting system. Automated transfer as in the case of stereotactic VAB is not possible.

**MRI-guided vacuum-assisted biopsy**

While only the Mammotome® (Devicor Inc., Cincinnati, USA) was available during the early years of MRI-assisted biopsy in the late 1990s, multiple manufacturers now offer equipment for MRI-guided VAB of the breast. In addition to the Mammotome®, the ATEC® (Hologic Inc., Bedford, USA), Vacora® (Bard GmbH, Karlsruhe, Germany) and EnCor™ (Senorx or Enspire, Bard GmbH, Karlsruhe, Germany) are Europe’s most widely used biopsy devices. MRI-guided VAB was originally performed using an 11-gauge (G) needle. As in stereotactic VAB, MRI-guided vacuum-assisted biopsy has trended toward larger needle gauges (10G–7G), since these allow the collection of the same tissue volume with fewer individual samples [18], thereby possibly shortening the examination time. For stereotactic VAB, the current S3-guideline recommends taking at least 12 10G samples or an equivalent tissue volume if other needle gauges are used [4]. The S3-guideline does not define a number of samples for MRI-VAB, but a European consensus paper on the use of MRI-VAB recommends taking at least 24 11G samples or an equivalent tissue volume if larger needle gauges are used [5]. However, the recommended numbers of mammography-guided stereotactic vacuum-assisted biopsy samples were simply adopted here, since there are no studies regarding the sufficiency of MRI-VAB as a function of the number of samples.

Most VAB devices have a cable connection to the vacuum source located outside the MRI examination room. The Vacora® is the only battery-operated system and thus the only...
true handheld system. The disadvantage of this system is that the device has to be removed from the breast after each sample is taken. While the Mammatome® also takes individual samples, the biopsy system remains in the breast during the entire intervention. The samples are transported to a chamber in the handle, where they can later be removed. The ATEC® and EnCor™ provide the advantage of the automated removal of multiple samples in immediate succession. The ATEC® additionally provides the option of rinsing the biopsy cavity with saline. Finally, all of these devices deliver satisfactory precision and provide reliable sampling (Table 1).

Following MRI-VAB, it is necessary to verify whether the tissue sampling was successful, i.e., whether at least portions of the targeted lesion have been removed. In this process it should be documented whether the biopsy was representative, questionably representative or not representative [5]. According to the recommendations of the Breast Diagnostics Working Group of the German X-ray Society, MRI-VAB is representative if the findings are smaller in size or no longer detectable or if the location of the resection bed is representatively in the area of the non-visible lesion [15]. Due to increasing contrast enhancement of the surrounding parenchyma and wash-out of the suspected lesion, the latter often cannot be identified with certainty in the post-interventional T1-w GE-series. Transferring a region-of-interest (ROI) that has been drawn prior to intervention to the post-interventional image series is helpful for evaluating biopsy results. Because lesion dislocation (e.g. caused by a hematoma) can potentially occur, resulting in incorrect transfer of the ROI to the post-interventional image series, additional anatomic structures should be used for evaluating biopsy results. According to an interdisciplinary European consensus recommendation, contrast medium can be readministered to improve biopsy result evaluation [5]. However, bleeding and resulting contrast enhancement in the biopsy cavity can hamper immediate post-interventional evaluation. In addition, interventional MRI image quality is often inferior to that of diagnostic MRI. A general recommendation regarding the performing of another contrast-enhanced MRM following MRI-VAB cannot be derived from the data published to date. However, a follow-up MRI after 24 hours would be advisable at least in the case of questionably representative MRI-VAB [19]. To keep the risk of developing nephrogenic systemic fibrosis (NSF) low, this approach should optimally be considered only in patients with healthy kidneys and when using stable contrast mediums with a low risk of NSF (macrocyclic gadolinium chelates).

All MRI-VAB should be presented and discussed in an interdisciplinary conference [5]. The correlation of the histopathological diagnosis with the imaging should be determined and the further procedure should be specified. In the case of a representative MRI-VAB of a BI-RADS® 4 or 5 lesion with a correlating, benign histopathological diagnosis (e.g. lymph nodes, fibroadenoma, mastitis, focal tumor-like adenosis), a single follow-up MRI examination should be performed after 6 to 12 months [4, 5].

**Table 1** Success and malignancy rates of MRI-guided vacuum-assisted biopsy in selected publications from the past 10 years with number of cases n> 50 [26, 28, 35, 39 – 43].

<table>
<thead>
<tr>
<th>publication</th>
<th>number</th>
<th>needle gauge [G] and equipment</th>
<th>mean lesion size</th>
<th>malignant</th>
<th>benign</th>
<th>lesions at risk1</th>
<th>non-representative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perlet et al. 2002</td>
<td>341</td>
<td>11 G/Mammatome®</td>
<td>–</td>
<td>84 (25 %)</td>
<td>233 (70 %)</td>
<td>17 ADH (5 %)</td>
<td>7 (2 %)</td>
</tr>
<tr>
<td>Liberman et al. 2005</td>
<td>98</td>
<td>9 G/ATEC</td>
<td>10 mm</td>
<td>24 (24 %)</td>
<td>52 (53 %)</td>
<td>10 (10 %)</td>
<td>3 (3 %)</td>
</tr>
<tr>
<td>Perlet et al. 2006</td>
<td>538</td>
<td>11 G/Mammatome®</td>
<td>–</td>
<td>138 (27 %)</td>
<td>362 (70 %)</td>
<td>17 ADH (3 %)</td>
<td>21 (4 %)</td>
</tr>
<tr>
<td>Orel et al. 2006</td>
<td>85</td>
<td>9 G/ATEC®</td>
<td>17 mm</td>
<td>52 (61 %)</td>
<td>15 (18 %)</td>
<td>18 (21 %)</td>
<td>2 (2 %)</td>
</tr>
<tr>
<td>Mahony et al. 2008</td>
<td>55</td>
<td>10 G/EnCor™</td>
<td>10 mm</td>
<td>10 (18 %)</td>
<td>38 (69 %)</td>
<td>7 (13 %)</td>
<td>0</td>
</tr>
<tr>
<td>Malhaire et al. 2010</td>
<td>72</td>
<td>10 G/Vacora®</td>
<td>Median: 12 mm</td>
<td>33 (46 %)</td>
<td>29 (40 %)</td>
<td>10 (14 %)</td>
<td>2 (2 %)</td>
</tr>
<tr>
<td>Fischer et al. 2009</td>
<td>389</td>
<td>9 G/ATEC®, 10 G/Vacora®</td>
<td>–</td>
<td>106 (27 %)</td>
<td>231 (59 %)</td>
<td>50 (13 %)</td>
<td>0</td>
</tr>
<tr>
<td>Oxner et al. 2012</td>
<td>187</td>
<td>10 Gauge/Vacora®</td>
<td>Range: 4 – 12 mm</td>
<td>44 (24 %)</td>
<td>126 (68 %)</td>
<td>15 (8 %)</td>
<td>–</td>
</tr>
</tbody>
</table>

1 Benign lesions with unclear biological potential (B3): atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), lobular neoplasia (LN), radial scars/complex sclerosing lesions, papillary lesions, suspected phyllodes tumor.

Clip marking following MRI vacuum-assisted biopsy

Like stereotactic VAB, clip marking following MRI-VAB is advisable especially in the case of small lesions, since they can frequently be removed entirely or to a great extent by VAB [5]. In the case of benign findings as well, an implanted clip can be useful for relocating the biopsied lesion on follow-up MRI. In addition, MRI-guided marking of surgery-relevant corner points following representative MRI-VAB is advisable in cases of extensive cancer findings and planned breast-conserving therapy, particularly when segmental or regional contrast enhancement is present (BI-RADS®, “non-mass-like enhancement”). Numerous manufacturers offer a wide assortment of MRI-compatible clips. Specifically developed clips are available from the respective manufacturer for each of the VAB devices presented in this article with the exception of the Vacora®. Using these clips is recommended for achieving optimal compatibility with the guide needle. A mammogram should be performed in two views to check the clip location [5, 15]. Like stereotactic VAB, MRI-VAB entails the risk of clip dislocation. Therefore, it is necessary to ensure correlation of the location of the clip and lesion [20].

MRI-guided lesion marking

Primary MRI-guided lesion marking with subsequent excision biopsy should only be performed for the histological confirmation of suspected lesions visible exclusively on MRI...
if MRI-VAB is not possible [4, 5]. This can be the case, for example, when the lesion is in an unfavorable location (close to the thoracic wall or nipple) or when implants are present. Various MRI-compatible metal wires or clips from numerous suppliers as well as metal coils (MReye® breast localization coil, Cook, Bjaerverskov, Denmark) can be used as markers. Clips and coils can be preoperatively localized using ultrasound- or mammography-guided wire marking. One advantage of clips and coils over the relatively soft MRI-compatible wires is that they remain securely in position in the breast, resulting in a lower incidence of secondary dislocation in our experience. After the completion of MRI-guided lesion marking, the position of the marker should be checked by means of two-view mammography [5, Fig. 4).

Findings not visible on interventional MRI

According to the literature, 2–16% of interventions are discontinued due to lesions no longer visible on MRI [25–29]. If BI-RADS® 4 or 5 findings detected on diagnostic MRI are no longer visible, it is necessary to first rule out technical causes. For example, strong breast compression may result in hyperintense findings and be interpreted as lesions of increased contrast medium enhancement [24]. To avoid such false findings, the unsubtracted series should also be included in the evaluation [23]. If the artifacts are so severe that reliable diagnostic evaluation is not possible, MRI should be repeated to reveal any false-positive findings and reduce the number of unnecessary MRI interventions.

Pitfalls – False findings on diagnostic MRM

Hormonal stimulation and motion artifacts can cause false findings on MRI. In fact, a recently published study showed an increase in false-positive findings of 17% when premenopausal patients were examined at a time other than during the second week of their menstrual cycle [21]. If diagnostic MRI is performed at the incorrect point in the menstrual cycle in premenopausal women or during hormone replacement therapy in postmenopausal women and if a hormonal cause for the contrast enhancement is suspected, another MRM should be performed [5, 16]. This applies particularly for BI-RADS® 4 findings that do not present as space-occupying focal findings (BI-RADS®: “mass”) but rather as segmental or regional contrast enhancement (BI-RADS®: “non-mass-like enhancement”). To reduce hormone-based contrast enhancement and minimize false-positive findings, the examination should be adapted to the patient’s menstrual cycle, ideally being performed during the second week of the cycle [22, 23]. Hormone replacement therapy in postmenopausal women should be suspended four weeks prior to the subsequent MRM. Patients undergoing MRM for local staging of a known breast carcinoma should be re-examined only if doing so would not result in any relevant delay of the planned treatment.

In the subtraction images of the T1-weighted contrast enhanced series, motion artifacts can result in hyperintense findings and be interpreted as lesions of increased contrast medium enhancement [24]. To avoid such false findings, the unsubtracted series should also be included in the evaluation [23]. If the artifacts are so severe that reliable diagnostic evaluation is not possible, MRI should be repeated to reveal any false-positive findings and reduce the number of unnecessary MRI interventions.

Fig. 4 61-year-old patient with mammographically detected 10-mm BI-RADS® 4 microcalcification in the right breast at the 12 o’clock position 5 mm from the nipple, histology indicating ductal carcinoma in situ of intermediate nuclear grading (G2). Preoperative breast MRI due to limited ability to evaluate mammography and ultrasound. Right-sided maximum intensity projections (a transverse, b sagittal) of the early subtraction series (T1w-GE) with suspicious contrast enhancement measuring 60 mm in diameter in the center of the right breast. MRI-guided marking of the cranialateral and dorsosmedial lesion edges using coils prior to breast-conserving therapy. Post-interventional mammography in craniocaudal c and d mediolateral projection with visualization of microcalcifications and MRI marking material. The double preoperative sonographic wire marking of the coils and mammographic imaging prior to segment resection are not shown. Histology: Two invasive ductal breast cancers (T1c, 20 mm, G2) and accompanying DCIS (G2) measuring 40 mm in diameter.
Minimum number of MRI-guided interventions

EUSOMA (European Society of Breast Cancer Specialists) requires a minimum of 10 MRI-guided breast interventions per year [23]. This is in accordance with the recommendations of an international consensus paper on MRI-VAB [5], which requires 15 MRI-VABs for learning the procedure and 10 MRI-VABs for maintaining competence. At a German consensus conference, all participants favored minimums for performing MRI-guided breast interventions, with most advocating a minimum of > 25 MRI interventions per year [16].

Results in the literature

According to more recent studies, histologically confirmed lesions visible only on MRI have a malignancy rate of 22–33%, which varies depending on the patient cohort examined and the MRI evaluation criteria employed [8, 32–35]. In these studies, MRI-guided lesion marking proved to be a valid and precise method [36]. Larger studies involving > 50 lesions have reported technical success rates of 97–98% [30, 37, 38]. However, MRI-guided lesion marking has since been replaced by MRI-VAB and is only warranted in isolated cases (see above). Table 1 shows an overview of the success and malignancy rates of MRI-VAB [26, 28, 35, 39–43]. Overall, MRI-VAB has a very high success rate of 96–100% regardless of lesion size and needle size (11–9G). The malignancy rate is between 18% and 61% with a mean of 28%, and the incidence of benign lesions exhibits a similar range of 18–70% with a mean of 62%. High-risk lesions, i.e., benign lesions with unclear biological potential (B3), were detected in 21% of cases [40]. In such cases, the further treatment plan must be defined on an interdisciplinary basis. For example, the diagnosis of a radial scar or complex sclerosing lesion through vacuum-assisted biopsy generally results in a classification of B3 and is an indication for excision biopsy [4].

MRI-VAB is associated with a very low complication rate. In the largest multicenter study published to date, Perlet et al. [35] reported that complications occurred in only 17 of 538 (3%) MRI-VABs using an 11G needle. Specifically, these cases involved five vasovagal reactions, one infected hematoma, six large hematomas (> 3 cm) and five cases of significant bleeding during the intervention, two of which required surgical hemorrhage. A more recent study involving 389 MRI-VABs using 9G and 10G needles [28] reports an even lower complication rate of 1% (n = 4). Two cases involved post-interventional secondary hemorrhage, while the other two cases concerned pain persisting for more than seven days. Overall, the complication rates of MRI-VAB are comparable to those of mammography-guided stereotactic vacuum-assisted biopsy, the latter being described as having complication rates of 1.8% and 1.3% in larger study cohorts of 500 and 1,114 patients, respectively [44, 45].

Conclusion

Suspicious breast lesions detectable only on MRI (BI-RADS® 4 and 5) should be histologically confirmed by MRI-guided intervention. It must be demonstrated beforehand that these lesions cannot be clarified using other image-guided methods (mammography/ultrasound). In addition, the presence of false findings must be ruled out. MRI-VAB is a very safe procedure with an extremely low complication rate and it should be used as the method of first choice for clarifying MRI-BI-RADS® 4 and 5 findings. MRI-guided lesion marking with subsequent surgical biopsy should be used only in exceptional cases for clarifying suspicious MRI findings, e.g., if MRI-VAB is not possible. MRI-guided marking of surgery-relevant corner points can serve to better define the target volume in cases of extensive cancer findings without mammographic or sonographic correlation. If BI-RADS® 4 and 5 findings visible only on MRI are not detectable on interventional MRI, a follow-up MRI should be performed within six months. For premenopausal women, the procedure should optimally be scheduled during the second week of the menstrual cycle.

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