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INVITED REVIEW

MRI-detected breast lesions: clinical implications and evaluation based on MRI/ultrasonography fusion technology

Kazuaki Nakashima[1] · Takayoshi Uematsu[1] · Taiyo L. Harada[1] · Kaoru Takahashi[2] · Seiichirou Nishimura[2] · Yukiko Tadokoro[2] · Tomomi Hayashi[2] · Junichiro Watanabe[3] · Takashi Sugino[4]

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Abstract
Magnetic resonance imaging (MRI) is a highly sensitive imaging modality that frequently reveals additional breast lesions that are occult on mammography and ultrasonography (US) and are thus difficult to diagnose. It is important to investigate these MRI-detected suspicious lesions, which are associated with a fairly high rate of malignancy. In this review, we have discussed MRI/US fusion technology, a magnetic position tracking system that synchronizes real-time US and MRI to improve lesion detection and enables comparisons of MRI and US findings of the detected lesions. This combination increases the precision of second-look US. We hope that our review underscores the importance of understanding the US findings and histopathology of MRI-detected breast lesions, as this will enable radiologists to perform appropriate assessments.

Keywords Breast cancer · MRI-detected lesion · Second-look ultrasonography · Fusion · Real-time virtual sonography

Introduction

Contrast-enhanced magnetic resonance imaging (MRI) is a highly sensitive method (86–100%) for the detection of breast cancer. Accordingly, MRI frequently identifies additional breast tumors that are occult on mammography and ultrasonography (US) [1, 2] (Fig. 1). However, the variable specificity (20–100%) of MRI can increase the difficulty of patient management. Particularly, it is often difficult to determine the management of breast lesions that are detectable using MRI but occult via other modalities. MRI-guided biopsy, which is used to diagnose MRI-detected lesions, has been covered by the Japanese insurance system since 2018. However, the application of MRI-guided biopsy is presently limited by several barriers. Particularly, this method is expensive, time-consuming for both patients and radiologists, and requires both specialized equipment and adjustments to MRI schedules.

A profound understanding of MRI-detected lesions has become increasingly important since the approval of health insurance coverage for MRI-guided biopsy. MRI/US fusion technology, including real-time virtual sonography (RVS, Hitachi Ltd.), provides an alternative approach to the detection of breast lesions [3–8]. This modality improves lesion detectability on US and enables accurate evaluation of the US findings of MRI-detected lesions. In this review, we have demonstrated the ultrasonographic and histopathological findings of MRI-detected lesions and discussed the appropriate management of these lesions.

MRI-detected breast lesions

In a meta-analysis [9], contrast-enhanced MRI detected additional ipsilateral tumor foci in a median of 16% (range 6–34%) of patients with breast cancer. Furthermore, Pediconi et al. [10] prospectively assessed 118 patients with unilateral cancers or high-risk lesions and reported that contralateral breast cancers could be detected in 22 patients (19%) by MRI alone at the time of unilateral cancer

✉ Kazuaki Nakashima
kaz.nakashima@scchr.jp

[1] Department of Breast Imaging and Breast Interventional Radiology, Shizuoka Cancer Center Hospital, Nagaizumi, Shizuoka 411-8777, Japan

[2] Department of Breast Surgery, Shizuoka Cancer Center Hospital, Shizuoka, Japan

[3] Department of Breast Oncology, Shizuoka Cancer Center Hospital, Shizuoka, Japan

[4] Department of Pathology, Shizuoka Cancer Center Hospital, Shizuoka, Japan

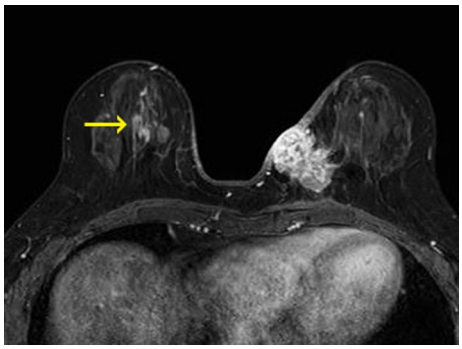

Fig. 1 A 63-year-old woman with cancer in the left breast. MRI reveals segmental non-mass enhancement (arrow) in the contralateral right breast that was not visible using mammography and ultrasonography

diagnosis. Of these 22 contralateral breast cancers, 14 (64%) were classified as ductal carcinoma in situ (DCIS) or lobular carcinoma in situ. Similarly, Fausto et al. [8] reported the detection of 722 additional breast lesions, including 273 (38%) malignant and 449 (62%) benign lesions, in 490 (25%) of 1930 MRI examinations.

Only MRI-detected breast lesions are defined as those not visible on mammography and US. These lesions are difficult to diagnose because conventional mammography- or US-guided biopsy cannot be applied. However, the prevalence of malignancy among these MRI-detected lesions is not negligible, with reported rates ranging from 2 to 51% [11]. Accordingly, these lesions cannot be dismissed. Uematsu et al. [5] reported a malignancy rate of 39% in a sample of 74 MRI-detected lesions, including 16 invasive carcinomas and 13 DCIS as well as benign lesions such as fibrocystic changes ($n=29$), fibroadenomas ($n=10$), papillomas ($n=3$), sclerosing adenosis ($n=2$), and granuloma ($n=1$). Tozaki et al. [12] further demonstrated that 36 (35%) of 102

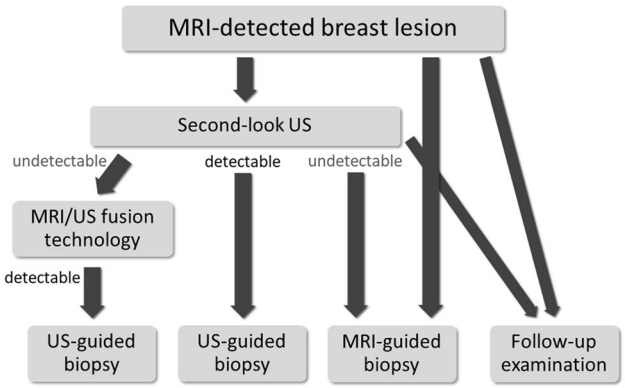

Fig. 2 Flowchart of the assessment process for MRI-detected lesions. Second-look US is a first step toward the further assessment of MRI-detected suspicious lesions. When the lesion is detectable on second-look US, it can be histologically verified via US-guided biopsy. When the lesion is undetectable on second-look US, MRI-guided biopsy is recommended. Recent MRI/US fusion technology and subsequent US-guided biopsy may be an alternative to MRI-guided biopsy. When an MRI-detected lesion is assessed as BI-RADS category 3 or less on MRI or second-look US findings, follow-up examination is acceptable. *US* ultrasonography, *BI-RADS* Breast Imaging Reporting and Data System

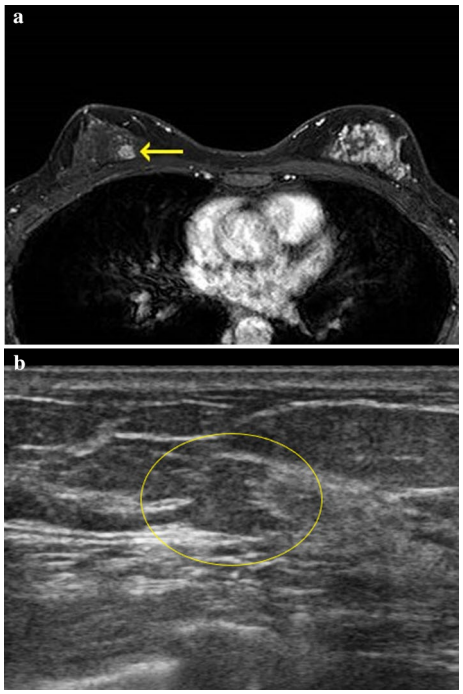

Fig. 3 A 47-year-old woman with cancer in the left breast. **a** Post-contrast MRI reveals focal non-mass enhancement (arrow) in the right breast. **b** The MRI-detected lesion is identified on second-look ultrasonography

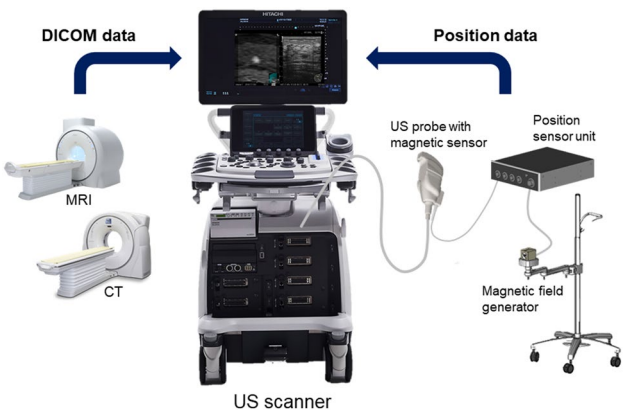

Fig. 4 MRI/US fusion system, including a magnetic field generator, position sensor unit, and US probe with magnetic sensor. MRI data in DICOM format and positional information acquired using the magnetic generator and magnetic sensor on the US probe are transferred to the US machine. MR and US images are then synchronized and displayed simultaneously on the US monitor

MRI-detected lesions subjected to MRI-guided biopsy were found to be malignant.

Currently, there is no consensus regarding the further assessment of MRI-detected lesions. Figure 2 presents acceptable assessments of these lesions. In summary, needle biopsy is required for the definitive diagnosis of a suspicious MRI-detected lesion when it cannot be assumed to be background parenchymal enhancement or a benign lesion, given the possibility of malignancy.

Second-look US

Second-look US is defined as a targeted US examination of lesions that were not initially detected on US but were later detected using other modalities, mainly MRI (Fig. 3). This examination has been accepted widely as a first step toward the further assessment of MRI-detected lesions [8, 11, 13, 14], and identified lesions can be verified histologically after US-guided biopsy. In a previous study, a mean of 58% (range 23–82%) of MRI-detected lesions could be identified using second-look US [11]. Furthermore, Abe et al. [13] reported that 115 (57%) of 202 MRI-detected lesions were detectable on second-look US, including 33 malignant and 82 benign lesions; the remaining 87 (43%) lesions were not correlated sonographically. DeMartini et al. [14] reported that 76 (46%) of 167 MRI-detected lesions could be identified on second-look US.

Several clinical and imaging features of lesions detectable using second-look US have been identified. Malignant and mass lesions are significantly more likely than benign and non-mass lesions, respectively, to be identified using second-look US [11, 13–16], and particularly, the majority of MRI-detected "mass" lesions can be identified on second-look US. Conversely, an MRI-detected suspicious lesion without mass enhancement is frequently not detected on US [13, 14, 16]. In a previous analysis, Spick et al. [11] reported that when an MRI-detected lesion was identified by second-look US, the positive predictive value for malignancy was 31%. Conversely, when an MRI-detected lesion could not be identified by second-look US, the negative predictive value was 88%. Abe et al. [13] further reported that the correlation rate for mass lesions increased with increasing lesion size. In contrast, however, DeMartini et al. [14] did not find an association of lesion size with the lesion detection rate.

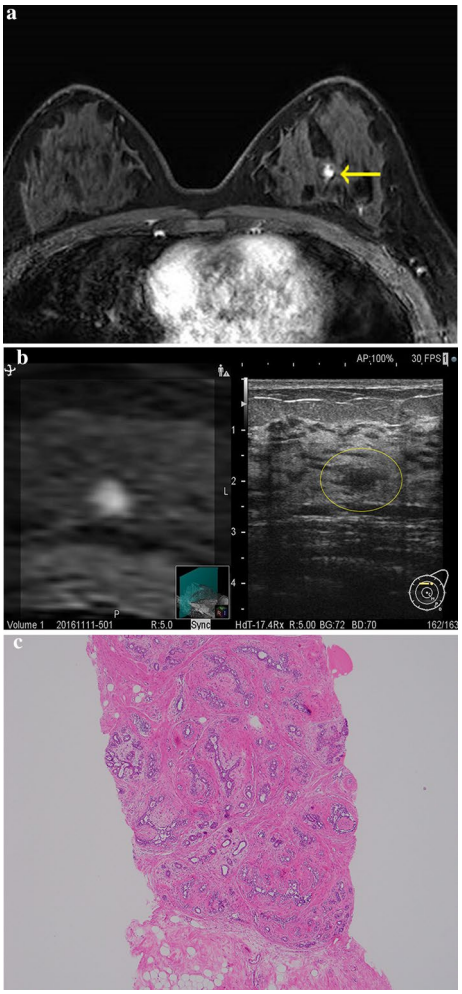

Fig. 5 A 35-year-old woman with axillary lymphadenopathy. **a** Post-contrast MRI shows focal non-mass enhancement (arrow) in the left breast, which was occult on mammography and ultrasonography. **b** The lesion is identified using MRI/US fusion technology. **c** The fusion image-guided biopsy specimen indicates fibroadenoma

Unfortunately, the lesion detection rates associated second-look US vary widely, with reported values of 23–82% [11]. As the US findings of MRI-detected lesions are often subtle, the success of second-look US is highly dependent

Table 1 MRI/US fusion detection of MRI-detected lesions and histopathology of the fusion image-detected lesions

Study	No. of patients	Lesion detection rate		Histopathology of MRI/US fusion-detected lesion	
		Second-look US (%)	MRI/US fusion (%)	Malignant (%)	Benign (%)
Nakano et al. 2012 [24]	67	30	90	23	77
Pons et al. 2014 [4]	43	43	91	35	65
Uematsu et al. 2016 [5]	78	64	95	29	71
Watanabe et al. 2017 [6]	59	34	85	24	76

on the skill of the operator and the use of careful scanning techniques. Moreover, differences in breast position between MRI and US, which are performed in a prone and supine position, respectively, increase the difficulty of lesion correlation. Hence, the absence of US correlation does not exclude malignancy. Demartini et al. [14] reported that sonographically occult lesions had a non-negligible probability of malignancy (22%) that would warrant biopsy, despite a lack of sonographic detection. Therefore, MRI-guided biopsy is indicated even when a suspicious lesion is not detected on second-look US.

MRI-guided biopsy

MRI-guided biopsy is a widely accepted sample collection method for the histological diagnosis of MRI-detected suspicious lesions that remained occult on second-look US. Previous studies of MRI-guided biopsy reported malignancy rates of 26–33% [2, 12, 17]. The Breast Imaging Reporting and Data System (BI-RADS) [18] reported cancer rates of 20–50% as a benchmark for MRI-guided breast biopsy. Another study reported false negative rates ranging from 0 to 17% [19]. Although MRI-guided biopsy is described as safe and accurate, it remains complicated by several issues, including high financial and time burdens, a lack of availability, a requirement for contrast medium injection, and increased difficulty associated with lesions in locations such as proximal to the chest wall or the nipple [8, 17]. Moreover, MRI-guided biopsy may be aborted because of patient discomfort associated with the prone position and breast compression, an acute reaction to gadolinium-based contrast media, and an inability to visualize the lesion at the time of biopsy. Moreover, it is difficult to confirm adequate lesion sampling during MRI-guided biopsy because of the lack of real-time visualization of lesion removal during the procedure. The radiologic–pathologic correlation also frequently presents difficulties because contrast enhancement of the MRI-detected lesion can be visualized only in vivo and not in biopsy samples, in contrast to the use of calcifications to confirm the retrieval of stereotactic biopsy samples. Only a few papers have specifically analyzed the radiologic–pathologic concordance of suspicious MRI-detected lesions [17, 20].

Given the difficulty associated with the accurate validation of a benign result from MRI-guided biopsy, follow-up should be recommended even in the absence of

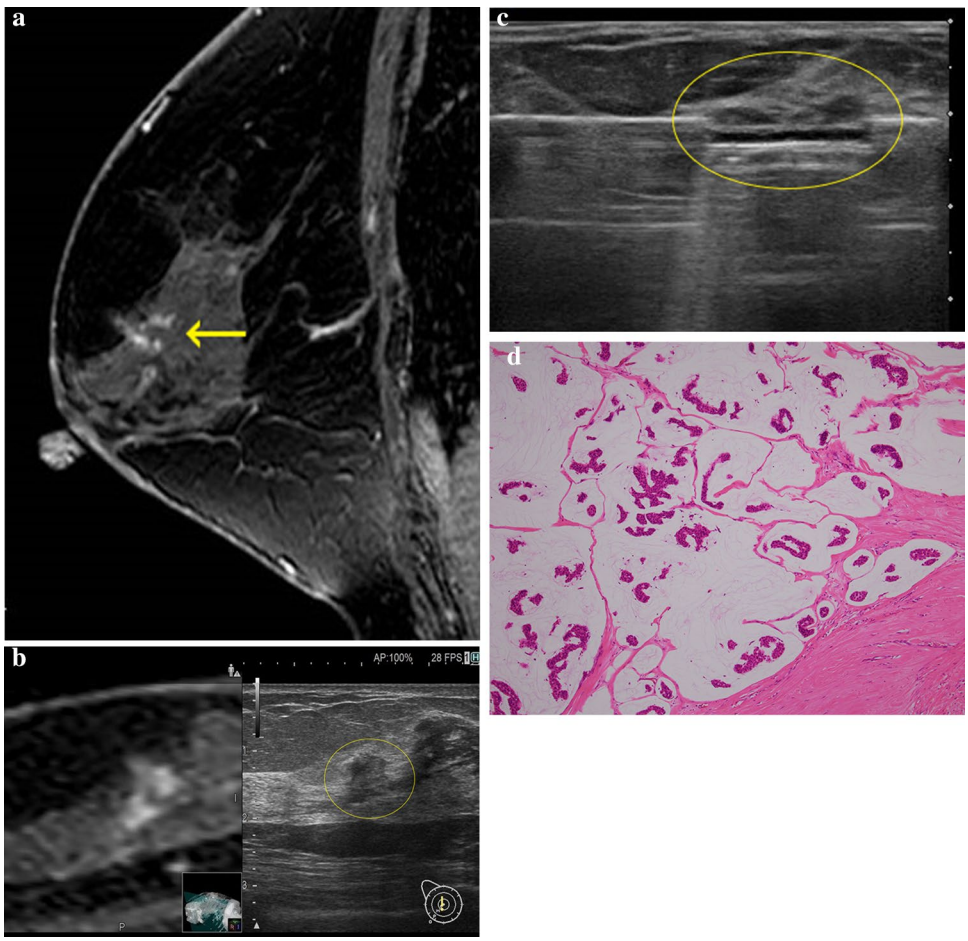

Fig. 6 A 64-year-old woman with post-operative cancer in the left breast. **a** The post-contrast MRI shows focal non-mass enhancement (arrow) in the right breast. **b** The MRI-detected lesion is identified using MRI/US fusion technology. **c** US-guided vacuum-assisted biopsy is performed. **d** The biopsy specimen reveals mucinous carcinoma

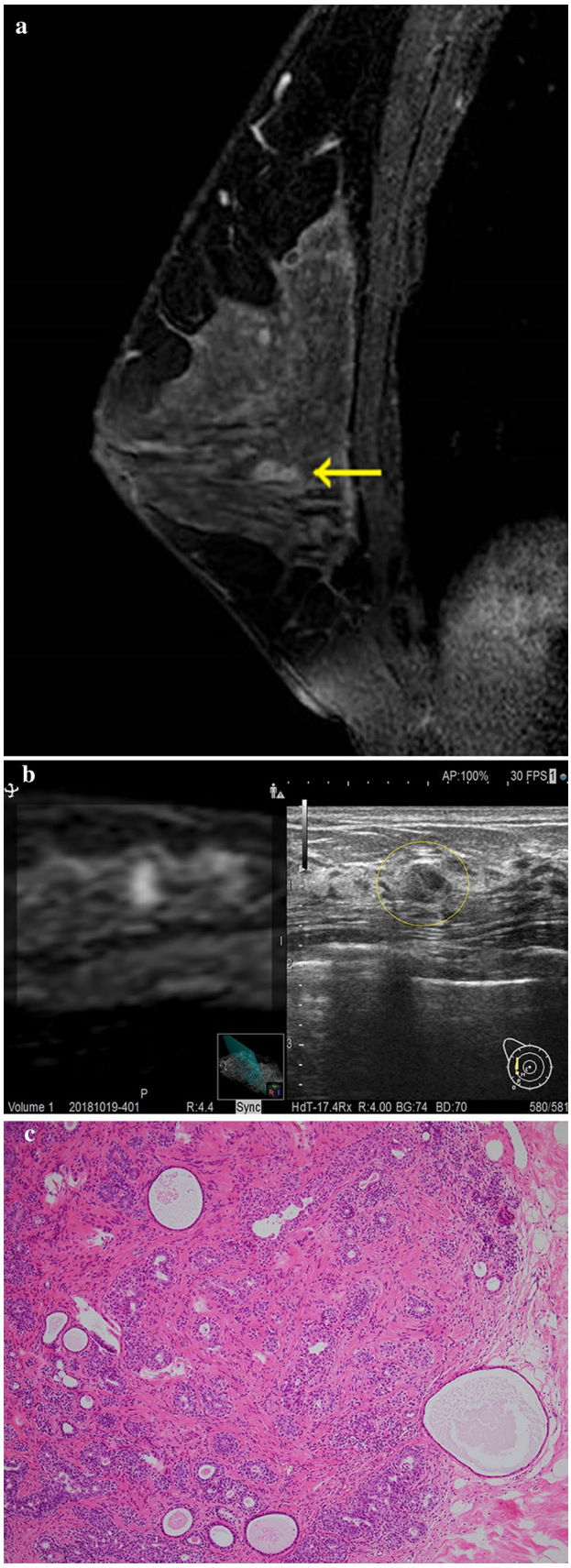

Fig. 7 A 49-year-old woman with cancer in the left breast. **a** The post-contrast MRI shows focal non-mass enhancement (arrow) in the contralateral right breast. **b** The MRI-detected lesion is identified on MRI/US fusion image. **c** The fusion image-guided biopsy specimen reveals mastopathy

radiologic–pathologic discordance or clinical suspicion [20]. A short-term follow-up MRI is routinely performed 6 months after a benign MRI-guided biopsy result [20, 21]. However, Li et al. [21] reported that cancers may remain stable at 6 months after biopsy, and other authors have argued that a 1-year follow-up is sufficient [22]. Follow-up MRI within 6–12 months detected subsequent cancers in 0.9–2.3% of lesions that received initially benign histopathology results by MRI-guided vacuum-assisted biopsy. This low rate of subsequent cancer development suggests that a short-term MRI follow-up may not be necessary. However, it may also be difficult to exclude malignancies during short-term follow-ups, as MRI-detected lesions are often only carcinoma in situ [5, 10, 12].

As noted above, MRI-guided breast biopsy has been covered by the Japanese insurance system since 2018, and a broader application of this procedure may solve some of the identified challenges. However, a member survey conducted by the European Society of Breast Imaging (EUSOBI) revealed that a minority (35%) of the participants had used MRI-guided breast interventions [23]. Although the use of MRI-guided biopsy has been recommended for institutions with a sufficient caseload of breast MRI, this survey demonstrates a different reality [23].

MRI/US fusion technology

MRI/US fusion technology, including RVS (Hitachi Ltd.), can be used to synchronize US with CT or MR images using a magnetic position tracking system, and can display both images simultaneously via multiplanar real-time reconstruction of the same section. This modality uses a commercially available US scanner, magnetic field generator, and magnetic sensor [5, 24] (Fig. 4). Any MRI and CT volume data in a digital imaging and communications in medicine format file can be transferred to the MRI/US fusion system. To date, this technique has been used to locate hepatic lesions that are difficult to recognize on conventional US or to treat such lesions via radiofrequency ablation [25, 26]. Recently, MRI/US fusion imaging of the breast has been applied as an option for identifying MRI-detected lesions [5, 6, 24] or presurgical planning [27].

Although Park et al. [28] reported improved detectability with second-look US even when using routine breast MRI

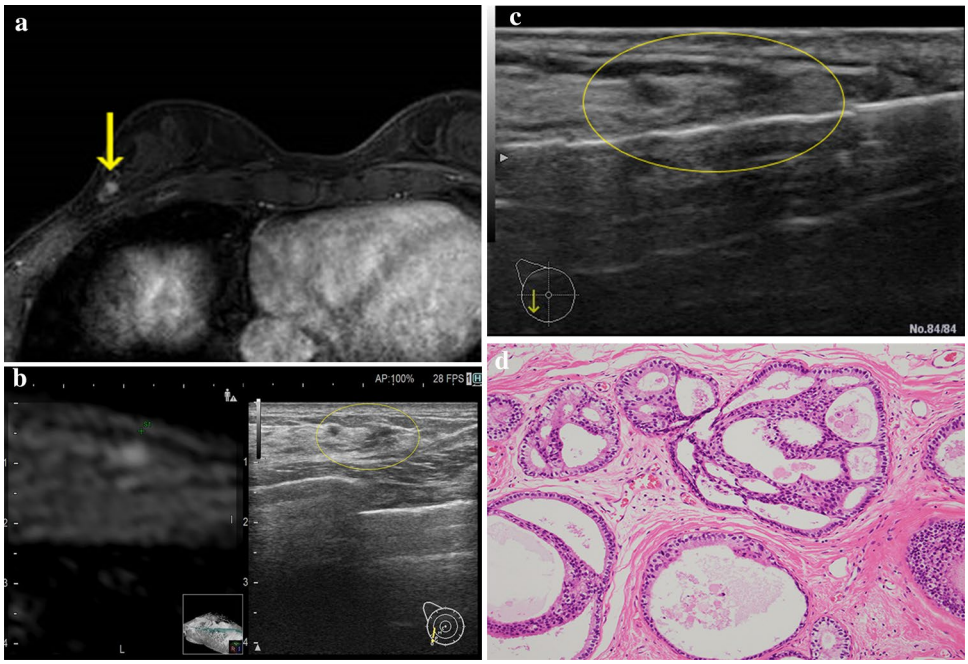

Fig. 8 A 57-year-old woman with sclerosing adenosis in the left breast. **a** Post-contrast MRI shows focal non-mass enhancement (arrow) in the contralateral right breast. **b** The MRI-detected lesion is identified on MRI/US fusion image. **c** US-guided vacuum-assisted biopsy is performed. **d** The biopsy specimen indicates low-grade ductal carcinoma in situ

in a prone position for fusion imaging, additional supine MRI is critical for minimizing the spatial displacement associated with second-look US [3, 6, 7, 29, 30]. A magnetic sensor mounted on the US probe can sense the magnetic field and detect the position and motion of the probe during scanning. Co-registration is a very important factor in the correct synchronization of lesion locations between two different modalities. In this regard, the nipple is currently recommended as the first reference point for co-registration [5, 7, 24], while blood vessels near the lesion could serve as a second reference point [7]. Other anatomical landmarks visible on US images, such as Cooper's ligaments, subcutaneous fat, and glandular tissue, can also be correlated with their locations on MR images.

MRI/US fusion technology has several strengths, including (1) improved detectability of second-look US, or "precise" second-look US; (2) the ability to recognize and evaluate US findings of the MRI-detected lesions; (3) and the ability to perform US-guided biopsy under real-time lesion visualization, rather than MRI-guided biopsy. Accordingly, more lesions are detected using MRI/US fusion than conventional second-look US [4–6, 24] (Table 1, Figs. 5, 6, 7, 8, 9, 10). As the latter can identify most MRI-detected "mass" lesions, non-mass lesions, rather than mass lesions, tend to require MRI/US fusion for detection [5]. MRI/US fusion technology is also superior for the identification of iso-echogenic breast lesions and those located within a heterogeneous background echotexture and/or around the mammary fascia or deep within the breast parenchyma [24, 28] (Figs. 5, 6, 7, 8, 9, 10). Park et al. [28] reported that cases involving lesions detectable by MRI/US fusion technology but not conventional US were more likely to exhibit a heterogeneous background echotexture and lesion iso-echogenicity on US and a middle or posterior lesion depth on MRI. As noted, the success of second-look US detection is highly operator dependent. The application of MRI/US fusion technology helps to reduce the skills gap between operators. Accordingly, this can be considered precise second-look US.

MRI/US fusion-guided biopsy

Once a MRI-detected lesion has been identified on MRI/US fusion images, US-guided biopsy can be performed using conventional biopsy techniques [31]. MRI-guided biopsy requires the use of an MRI room for 1–2 h, which hinders the performance of other MRI examinations. US-guided biopsy is, therefore, more desirable because, in addition to the lack of requirement for an MRI room, this technique is more broadly available, less costly and time consuming, and is associated with greater patient comfort. In the previous studies, the malignancy rates of the lesions subjected to MRI/US fusion-guided biopsy ranged from 23 to 35% [4–6, 24] (Table 1), and these rates were comparable with those associated with MRI-guided biopsy

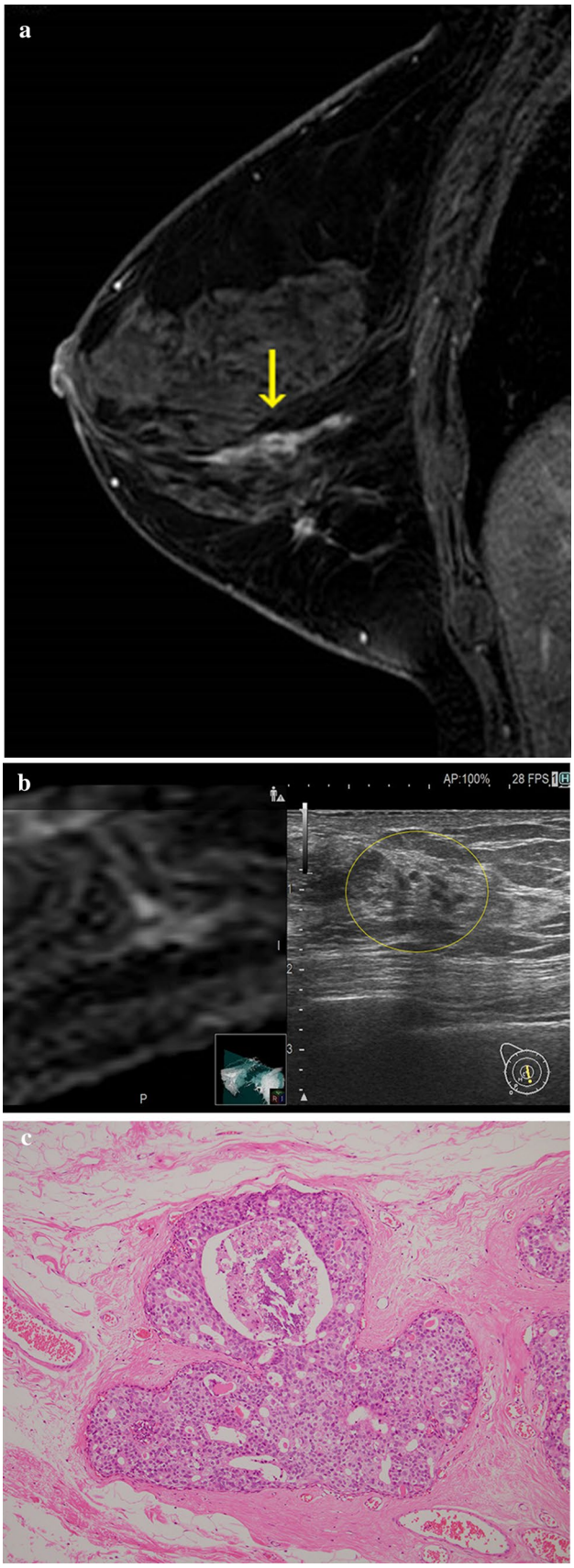

Fig. 9 A 63-year-old woman with cancer in the left breast. **a** Post-contrast MRI shows linear non-mass enhancement (arrow) in the contralateral right breast. **b** The MRI-detected lesion is identified on MRI/US fusion image. **c** The fusion image-guided biopsy specimen reveals intermediate-grade ductal carcinoma in situ

(26–33%) [2, 12, 17]. In a 6-year study, Faust et al. [8] reported that only 22 lesions required MRI-guided biopsy, in contrast to 151 lesions subjected to biopsy guided by MRI/US fusion technology. A significantly higher number of malignant lesions were found in the MRI/US fusion-guided biopsy group (56%) than that in required MRI-guided biopsy group (9%). No significant difference in lesion type (mass or non-mass enhancement) and lesion dimension was found between the two groups. Furthermore, although MRI-guided biopsy was mandatory for the lesions with breast hypertrophy, MRI/US fusion technology reduced the need for this procedure. In light of the EUSOBI survey, which demonstrated the lack of utilization of MRI-guided biopsies in clinical settings [23], MRI/US fusion-guided biopsy may provide an alternative for a large number of MRI-detected lesions, without incurring the expenses associated with MRI throughput. In Japan, MRI/US fusion technology may also be more favorable for the scanning and US–MRI correlation of the relatively small breast tissues of Japanese women.

After MRI/US fusion-guided biopsy, post-procedural breast MRI examinations is performed to determine successful lesion sampling by verifying that the targeted lesion has decreased in size or that a signal void of the biopsy marker is detectable at the lesion site (Fig. 10). However, the need for post-procedural MRI and the associated costs may be substituted by a careful evaluation of the radiologic–pathologic correlation and careful follow-up examinations [5].

Conclusions

MRI-detected breast lesions are associated with a non-negligible rate of malignancy and require further assessment. Although second-look US should be the first step toward a further assessment of these lesions, a negative result cannot exclude malignancy. Accordingly, MRI-guided biopsy should be performed for MRI-detected suspicious lesions that could not be correlated on second-look US. However, MRI/US fusion technology, including RVS, can improve the lesion detection rates and enable evaluations of the US findings of MRI-detected lesions. Moreover, MRI/US fusion-guided biopsy may be a viable

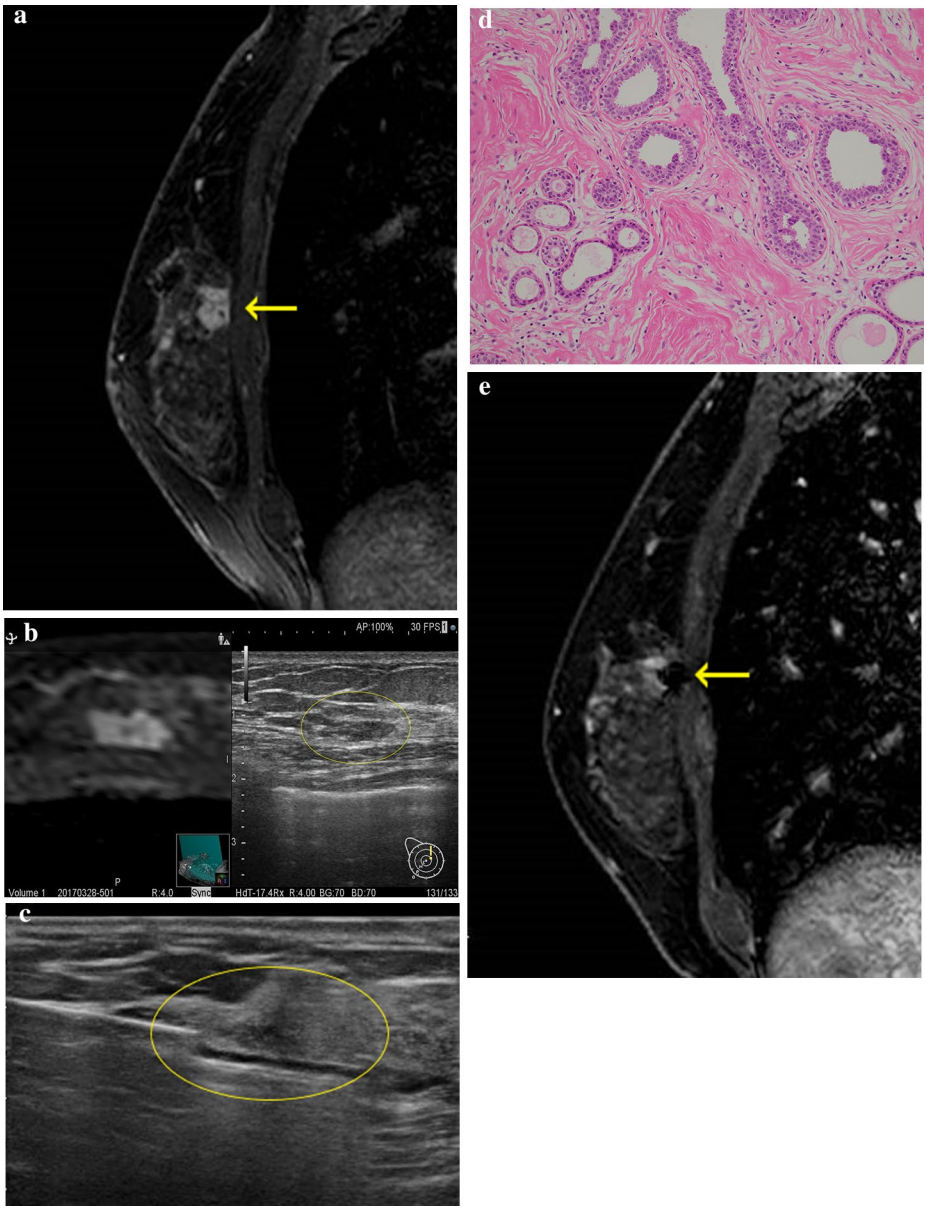

Fig. 10 A 47-year-old woman with cancer in the left breast. **a** Post-contrast MRI shows oval mass (arrow) in the contralateral right breast. **b** The MRI-detected lesion is identified on MRI/US fusion image. **c** US-guided vacuum-assisted biopsy is performed. **d** The biopsy specimen demonstrates mastopathy. **e** Post-biopsy MRI reveals a decrease in the size of the mass. A signal void corresponding to the biopsy marker is recognized at the lesion site (arrow)

alternative to MRI-guided biopsy. The accumulation of knowledge about the US findings associated with MRI-detected lesions may help to avoid unnecessary biopsies, thus reducing patient discomfort and medical costs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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