

Breast MRI: False-Negative Results and Missed Opportunities

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Abbreviations: BI-RADS = Breast Imaging Reporting and Data System, BPE = background parenchymal enhancement, CC = craniocaudal, DCIS = ductal carcinoma in situ, MIP = maximum intensity projection, MLO = mediolateral oblique, STIR = short τ inversion-recovery

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the broad categories of error in diagnostic radiology and the differences between perceptual errors and cognitive (interpretive) errors.
- Discuss strategies to improve lesion detection on breast MR images.
- Identify the features of certain subtypes of breast cancer in which a false-negative breast MRI result may occur owing to low-level enhancement or lesion nonenhancement.

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Breast MRI is the most sensitive modality for the detection of breast cancer. However, false-negative cases may occur, in which the cancer is not visualized at MRI and is instead diagnosed with another imaging modality. The authors describe the causes of false-negative breast MRI results, which can be categorized broadly as secondary to perceptual errors or cognitive errors, or nonvisualization secondary to nonenhancement of the tumor. Tips and strategies to avoid these errors are discussed. Perceptual errors occur when an abnormality is not prospectively identified, yet the examination is technically adequate. Careful development of thorough search patterns is critical to avoid these errors. Cognitive errors occur when an abnormality is identified but misinterpreted or mischaracterized as benign. The radiologist may avoid these errors by utilizing all available prior examinations for comparison, viewing images in all planes to better assess the margins and shapes of abnormalities, and appropriately integrating all available information from the contrast-enhanced, T2-weighted, and T1-weighted images as well as the clinical history. Despite this, false-negative cases are inevitable, as certain subtypes of breast cancer, including ductal carcinoma in situ, invasive lobular carcinoma, and certain well-differentiated invasive cancers, may demonstrate little to no enhancement at MRI, owing to differences in angiogenesis and neovascularity. MRI is a valuable diagnostic tool in breast imaging. However, MRI should continue to be used as a complementary modality, with mammography and US, in the detection of breast cancer.

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Introduction

Breast MRI has been increasingly used for both the detection and characterization of breast cancer. Breast MRI remains the most sensitive modality for the detection of breast cancer, with a reported sensitivity ranging from 77% to 96%, higher than the sensitivity of either mammography or US (1–10). This holds true for invasive carcinoma as well as for ductal carcinoma in situ (11). Furthermore, breast MRI is particularly valuable in women with an elevated lifetime risk of the disease ($\geq 20\%$), such as women who have an inherited genetic mutation or a history of mantle radiation therapy before 30 years of age (12). However, despite the benefits of breast MRI in the detection of cancer, false-negative cases may occur, in which breast cancer is not detected at MRI and is detected either at physical examination or at another imaging modality. In this article, we explore the causes of false-negative findings at breast MRI, as well as potential strategies to avoid similar diagnostic pitfalls in the future.

Breast Cancers Diagnosed Retrospectively at MRI

Several studies have demonstrated that signs of breast cancer may be overlooked at MRI, which may result in delayed diagnosis (4,10–15). For example, Pages et al (11) retrospectively reviewed

TEACHING POINTS

- Any dominant focus of enhancement demonstrating greater enhancement or an enhancement pattern different than that of the remaining foci should be viewed as suspicious.
- Radiologists should have a low index of suspicion to recommend biopsy in high-risk patients, as these patients may develop cancers with seemingly benign features.
- T2 hyperintensity must only be used as a criterion for attributing a benign cause when it is also associated with other benign imaging features, including benign morphology. A suspicious morphology, such as an irregular or spiculated mass, should always prompt the recommendation to perform biopsy, regardless of the T2 characteristics.
- Given that breast cancers may appear stable between examinations, it is critical that the radiologist uses all available prior comparison examinations when attempting to confirm relative stability of a lesion. Rather than reviewing only the most recent comparison prior examination, it is helpful to begin by first reviewing either the most remote prior examination or an examination from several years prior. The radiologist can then review the sequentially obtained prior examinations until reaching the most recent comparison examination when assessing for the stability of a finding.
- MRI should not be performed as a shortcut for resolving a true mammographically or sonographically suspicious finding in lieu of biopsy, as false negatives may occur.

the MRI examinations of patients diagnosed with breast cancer who had also undergone a prior breast MRI in which the findings were considered negative or benign. The authors found that in 28 of the 60 lesions (47%), an abnormality was visualized in retrospect that would have upgraded the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) classification of the prior MRI result to an actionable recommendation (11). A similar study was conducted by Seo et al (4), in which 72 consecutive negative prior MRI results were retrospectively reviewed in patients with subsequent MRI results with diagnosed breast cancer. The authors reported that of the 36 cases in which the findings were visible on the prior MR images, 33.3% of the lesions were deemed to be “actionable” (assessed as a BI-RADS category 4 or 5 by a majority of radiologists) at rereview (4).

Similar findings have been reported in studies assessing patients undergoing multiple rounds of screening breast MRI. A more detailed summary of these studies is shown in Table 1. In a study by Yamaguchi et al (13), of the 16 breast cancers diagnosed at screening MRI, nine cases were retrospectively visible on prior MR images and deemed to be false-negative cases (13). In a study by Maxwell et al (12) of high-risk women undergoing annual screening, the authors reported that 10 of the 23 women (43%) with prior breast MRI results available had a potentially avoidable delay in the diagnosis of breast cancer. Gubern-Mérida

et al (14) reported that in 40 patients undergoing screening breast MRI for elevated lifetime risk with an MRI-detected breast cancer, the lesion was retrospectively deemed to have been visible on the prior MR images in 24 of 40 cases (60%) (14). These findings are in line with results from the 22-center MARIBS study, in which 12 of the 16 incident cancers, as well as two interval cancers, were visible on prior MR images (10,15).

Despite studies demonstrating that breast cancer may be diagnosed retrospectively at MRI with some frequency, some authors have reported that the cancers on the prior false-negative breast MR images may have more favorable features than true-positive breast MRI cases diagnosed prospectively. For example, in a study by Shin et al (17), cancers deemed visible on prior false-negative MR images were associated with a lower BI-RADS classification at US (BI-RADS category 4a) than cancers detected initially with breast MRI. In addition, the authors reported a trend toward a lower T stage (“tumor” in the TNM classification system) of cancers initially missed at MRI as compared with cancers detected with MRI, although this was not statistically significant (17). This suggests that some false-negative breast cancers, despite their delay in diagnosis, may be associated with certain favorable features that do not necessarily result in a more suspicious BI-RADS category assessment or higher-stage tumor than true-positive breast MRI cases diagnosed prospectively.

Types of Error

Two broad categories of errors in diagnostic radiology have been identified: perceptual errors and cognitive (interpretive) errors (Table 2). Perceptual errors are the most common type of error in diagnostic radiology, reportedly accounting for 60%–80% of radiologists’ errors (18–20). A perceptual error occurs when an abnormality is identified only retrospectively and was not detected prospectively. The finding is simply not detected. Common causes of perceptual errors include (a) subtle findings, (b) the satisfaction of search phenomenon, (c) workplace distractions, (d) radiologist fatigue, and (e) poor lesion conspicuity, which may be due to the location of the abnormality at the edge of the field of view or on the first or last image of an MRI examination or caused by technical factors (20,21). Conversely, cognitive (interpretive) errors occur when an abnormality is identified prospectively but its significance is incorrectly interpreted, leading to an incorrect diagnosis. Common causes of cognitive errors include a lack of medical knowledge, radiologist bias, and incorrect or incomplete clinical information (18–21).

Table 1: Results from Selected Studies of Breast Cancers Diagnosed Retrospectively at MRI

Authors (Reference)	Patient Population	Time Between MRI Examinations	Results
Seo et al (4)	Patients with breast cancer who underwent MRI who had also undergone prior breast MRI with negative results	32.8 months (median)	In 36 of 72 cases when a finding was visualized retrospectively on prior MR images, 33.3% of the time it was classified as actionable (assessed as a BI-RADS category 4 or 5 by a majority of radiologists) on rereview
Magnetic Resonance Imaging Breast Screening (MARIBS) study (10), Gilbert et al (15)	High-risk patients undergoing annual MRI screening	Specific interval not reported	12 of the 16 incident cancers, as well as two interval cancers, were visible on prior MR images
Pages et al (11)	Patients diagnosed with breast cancer who underwent MRI and who had also undergone prior MRI in the previous 6–24 months for any cause (including high-risk screening, a history of breast cancer, or problem solving)	13.8 months (mean)	In 28 of 60 lesions (47%), an abnormality was visualized retrospectively that would have upgraded the BI-RADS category to an actionable recommendation
Maxwell et al (12)	High-risk patients undergoing annual MRI screening who had undergone prior breast MRI	Prior MRI screening within 2 years (exact interval not reported)	10 of 23 women (43%) who underwent prior breast MRI had a potentially avoidable delay in the diagnosis of breast cancer
Yamaguchi et al (13)	Patients undergoing several rounds of screening breast MRI	9.9 months (mean)	Nine of 16 cancers were retrospectively visualized on prior screening MR images
Gubern-Mérida et al (14)	High-risk patients undergoing MRI screening	11.6 months (mean)	In 24 of 40 cases (60%), the lesion was visualized retrospectively on prior MR images
Obdeijn et al (16)	High-risk patients undergoing annual MRI screening	Specific interval not reported	In nine of 21 patients, an abnormality was visualized retrospectively on the prior MR images, which should have changed the BI-RADS category assessment of the prior examination

In the following sections, we describe the potential sources of error at breast MRI and address strategies to prevent them. By identifying learning pearls and describing potential pitfalls in breast MRI examination interpretation, we hope that such missed opportunities can be prevented in the future.

Technical Factors Leading to False-Negative Results

Several technical factors have been reported that contribute to missed breast cancer at MRI, including patient motion artifact, inadequate intravenous contrast material injection, and tumor location at or beyond the field of view (Table 2). In a study by Teifke et al (2), these technical issues were the cause in five of 28 (17.9%) of the undetected

invasive breast cancers (22). Other studies have attributed an even larger percentage of false-negative breast MRI results to technical factors. Wurdinger et al (23) evaluated preoperative breast MRI results in patients with sequentially diagnosed breast cancers. The authors reported that of the 17 false-negative breast cancers that demonstrated contrast enhancement at MRI, nine (52.9%) were attributed to technical factors. In their study, these were most commonly due to previous core biopsy with bleeding artifact (hematoma or postbiopsy changes obscuring a cancer, $n = 3$), metal-induced artifact ($n = 3$), tumor location outside the field of view ($n = 1$), patient motion ($n = 1$), or inadequate contrast material injection ($n = 1$) (22).

Of the potential technical errors, patient motion is one of the most common causes of artifact

Table 2: Causes of False-Negative Breast MRI Results

Type of Error	Causes
Technical error	Patient motion
	Lack of intravenous contrast material administration (including unrecognized contrast extravasation)
	Incomplete or inadequate visualization of findings on images (including that due to poor patient positioning or secondary to a finding being located at the edge of or partially excluded from the field of view)
	Artifacts (including those from metal or hematoma)
Perceptual error	Failure to detect owing to blind spots or poor search patterns
	Poor lesion conspicuity (including poor conspicuity secondary to a complex background parenchymal pattern, obscuration or reduced visualization due to background parenchymal enhancement [BPE], or small lesion size)
	Subtle or atypical appearance of cancer
	Satisfaction of search
	Reader fatigue, distractions, or interruptions
Cognitive error	Stable or slowly growing lesion
	Lesions with seemingly benign features (including benign shape, morphology, or T2 hyperintensity)
	Attributing a suspicious finding as secondary to postsurgical change
	Incorrect or misleading clinical information
	Lack of knowledge (including recognizing that not all cancer subtypes may be visualized at MRI)
	Radiologist bias

(2). In their study of undetected malignancies at breast MRI, Teifke et al (2) assessed for both the presence as well as the degree of motion artifact at breast MRI. The authors reported that movement artifact was absent in only 36% of cases and found that, when present, patient motion was deemed to be weak in 45% of cases, medium in 12%, and strong in 7% (2). In one case, the authors reported that an invasive carcinoma was not visualized on the subtraction images owing to patient motion artifact and was visualized only in retrospect on the nonsubtraction images (2). Similarly, in their study of high-risk women undergoing screening breast MRI, Maxwell et al (12) reported that patient motion artifact may result in reduced conspicuity of cancers on subtraction images.

As such, during image review, it is critical to examine all MR images for adequate technique. Postcontrast (obtained after the administration of contrast material) images should be assessed to confirm appropriate intravenous contrast material injection. Visual inspection of the myocardium or mediastinal blood vessels is a simple way to ensure intravenous contrast material is present. If there is any doubt, a region of interest can be placed over the myocardium, with both precontrast (obtained before the administration of contrast material) and postcontrast values compared to ensure that contrast material has reached the venous system.

Similarly, the presence and degree of patient motion artifact should be assessed on nonsubtraction images before review of the subtraction images (24–26). Ensuring that the patient is as comfortable as possible before beginning the examination can help reduce patient motion artifact. Ideally, the MRI technologist should counsel the patient before the examination regarding the importance of remaining as still as possible and should also ensure patient comfort by helping secure the patient's arms and head in place with pillows (24). Some authors have reported improved technique by imaging the patient in an arms-down position rather than having the patient's arms extended above their head, citing that this position may be easier to hold (25).

When present, patient motion results in artifacts in the phase-encoding direction, which affects the entire series (24,26). If significant patient motion artifact is present, subtraction images may not be useful, as even minor patient motion may result in obscuration or false subtraction of tumors. Similarly, patient motion may result in misregistration artifact, in which motion between the pre- and postcontrast sequences results in the perceived enhancement at the subtraction sequences that is not present on the nonsubtraction postcontrast images (25,26). Because of this, the fat-suppressed postcontrast T1-weighted images should always be reviewed,

in addition to images obtained at the subtraction sequences, to ensure that small lesions are not missed secondary to motion artifact (12) nor are false areas of enhancement secondary to motion erroneously categorized as suspicious.

Perceptual Errors

Effect of Background Parenchymal Enhancement on False-Negative Cancer Diagnoses

Several studies have cited the obscuration of tumors by background parenchymal enhancement (BPE) as a factor in false-negative breast cancer diagnoses (2,16,17,27,28). More commonly, this has been found in the setting of moderate or marked BPE (27). In a study of patients undergoing screening breast MRI, Seo et al (4) retrospectively reviewed the prior negative screening MRI results of 72 patients with biopsy-proven breast cancer detected at subsequent screening MRI. Although all of the prior MRI results were reported as negative for malignancy, the authors found that in 36 of 72 cases (50%), the finding was visible on the prior MR images. Of these findings visible retrospectively, the authors attributed 27.8% (10 of 36 cases) as false negatives secondary to mimicking of physiologic enhancement (4).

Similar findings were reported by Shimauchi et al (28) in their study of 222 women with newly diagnosed breast cancer who underwent breast MRI for staging. The authors reported that only seven of 222 cancers were not visualized at MRI and attributed diffuse BPE as the cause in three of seven of these cases (42.9%). For the remaining four cases, the authors cited small size of the lesion ($n = 1$) and unknown reasons ($n = 3$) for the cancer nonvisualization (28).

Out of concern that BPE could obscure potential malignancy, some institutions recommend that nonemergent breast MRI be performed during the second week of the menstrual cycle (days 7–14) (27). However, other institutions, including our institution, do not routinely schedule based on a patient's menstrual cycle, as this creates complex patient logistical issues. Instead, at our institution, in the uncommon event that BPE is so marked that it obscures evaluation of the breasts, the patient may be recommended to return during days 7–14 of her menstrual cycle at the time of the patient's next screening MRI. Indeed, although some authors have cited BPE as a potential cause of false-negative results at breast MRI, other authors have reported no effect.

In a study by Yamaguchi et al (13) of breast cancers detected at incident screening breast MRI and patients who had previously received normal screening breast MRI results, the authors found

that of the nine false-negative results in their study, all cancers were previously visualized at MRI, regardless of the degree of BPE present on the prior images (13). Similarly, in a study by Hambly et al (29) of 250 women undergoing baseline high-risk screening MRI, the authors found no significant difference in either biopsy rate or cancer detection rate between the four BI-RADS categories of enhancement (minimal, mild, moderate, and marked). However, of note, the mild, moderate, and marked categories were associated with both a significantly higher rate of short-term follow-up (BI-RADS category 3, probably benign) and a lower rate of BI-RADS category 1 (negative) or BI-RADS category 2 (benign) assessments (29).

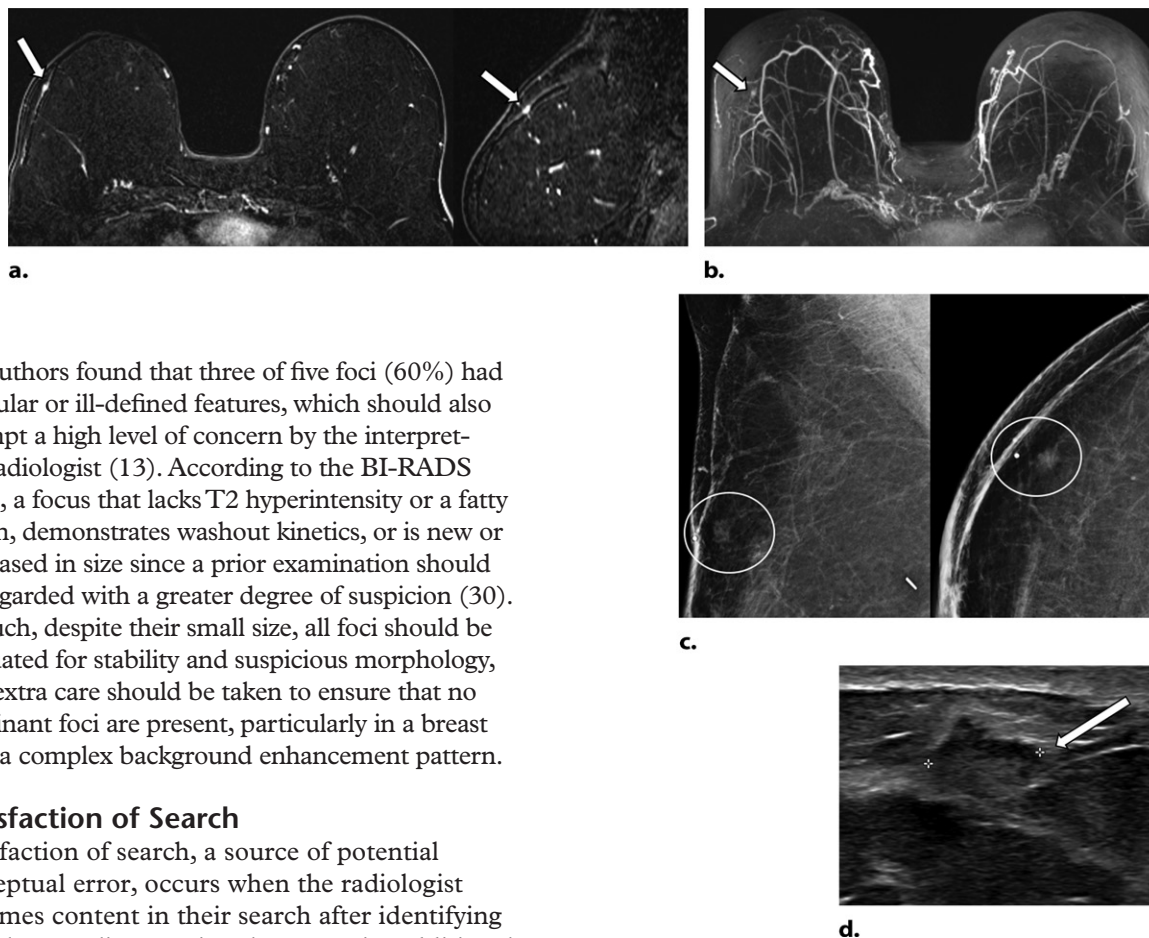
Small Lesion Size

Many authors have attributed small lesion size as a cause for false-negative breast cancers, with small lesions causing both perceptual and cognitive errors (2,13,16,17,28). A *focus* is defined as an area of contrast enhancement, usually less than 5 mm in size, that is neither a mass nor nonmass enhancement. Because of their small size, foci may be easily overlooked when interpreting MRI examinations, resulting in perceptual errors, as the radiologist simply does not visualize the abnormality owing to the small size (Fig 1). To combat this, careful review of the maximum intensity projection (MIP) images, as well as axial or sagittal reconstructed images, is critical, as small foci not apparent in one projection may become more visible when viewed in another imaging plane. A review of the first postcontrast sequences is also helpful for identifying small malignant lesions, as the difference in lesion-to-background enhancement is greatest at this time point (12).

Furthermore, when numerous foci of enhancement are present in the breasts, this may distract the radiologist, resulting in potential cognitive errors and missed cancer. Although bilateral symmetric scattered foci of enhancement represent a common pattern of BPE (27), the radiologist should pay careful attention to ensure that there is no dominant focus in the setting of other scattered foci. Any dominant focus of enhancement demonstrating greater enhancement or an enhancement pattern different than that of the remaining foci should be viewed as suspicious (Fig 2).

In a study by Yamaguchi et al (13), the authors found that of the nine false-negative results in their study, five of the eventual cancers were categorized as foci, and four of five of the foci were visible in the background of other foci on MR images. Of the four cancers visualized as foci in a background of other foci on MR images, 50% (two of four cases) were distinguishable from the additional foci on the images owing to higher signal intensity. In addition,

Figure 1. Failure to detect disease in a 50-year-old woman with a history of right breast cancer and bilateral mastectomy with bilateral free-flap reconstruction 7 years previously who underwent MRI for left chest wall pain. (a) Axial (left) and sagittal (right) T1-weighted fat-suppressed postcontrast subtraction MR images show a 4-mm enhancing focus (arrows) along the contact zone in the upper outer reconstructed breast. On the axial image (left), the focus lies along the contact zone, making it difficult to appreciate the finding as a discrete abnormality, and was not commented on by the radiologist. (b, c) Axial maximum intensity projection (MIP) image (b) shows the focus (arrow in b), which is slightly easier to visualize as a subtle separate focus. The patient presented 6 months later for evaluation of a palpable abnormality (circles in c), corresponding to the same site as the enhancing focus, as depicted on the electronically magnified mediolateral oblique (MLO) (left) and craniocaudal (CC) (right) mammograms (c). (d) US image shows an irregular hypoechoic mass (arrow) with an echogenic halo. The results of a biopsy confirmed recurrent invasive ductal carcinoma. Reviewing images obtained in all available planes and with all available sequences is critical, as small abnormalities may be more apparent on images in one imaging plane than in others.



the authors found that three of five foci (60%) had irregular or ill-defined features, which should also prompt a high level of concern by the interpreting radiologist (13). According to the BI-RADS Atlas, a focus that lacks T2 hyperintensity or a fatty hilum, demonstrates washout kinetics, or is new or increased in size since a prior examination should be regarded with a greater degree of suspicion (30). As such, despite their small size, all foci should be evaluated for stability and suspicious morphology, and extra care should be taken to ensure that no dominant foci are present, particularly in a breast with a complex background enhancement pattern.

Satisfaction of Search

Satisfaction of search, a source of potential perceptual error, occurs when the radiologist becomes content in their search after identifying one abnormality, causing them to miss additional abnormalities on the images (20,21). As such, it is critical to develop a set search pattern and not to deviate from this pattern (31). A thorough search pattern when interpreting breast MRI examinations should include not only evaluation of both breasts but also of other extramammary sites, including the bones, mediastinum, lungs, lymph nodes, and visualized portions of the upper abdomen, to avoid missing potentially significant nonbreast findings.

Cognitive Errors

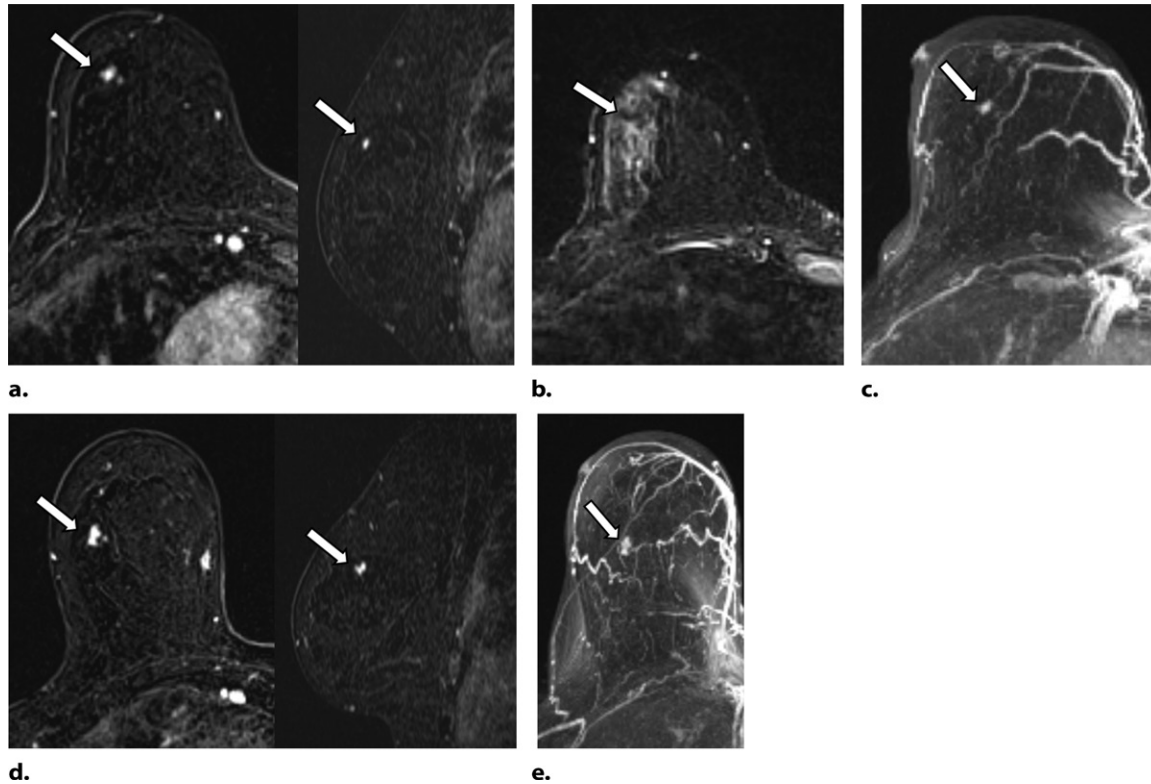
False-Negative Results Due to Perceived Benign Shape or Morphology

Although certain features of masses at MRI may suggest benignity, such as a round or ovoid shape, circumscribed margins, or “persistent” enhancement patterns, these features may also be associ-

ated with malignancy, particularly in patients who are *BRCA* mutation carriers (Fig 3) (12,15). In a study of patients who were *BRCA1* and *BRCA2* mutation carriers, up to 30% of cancers detected were round or oval or had smooth margins, and 24% of cancers had benign kinetic features. In addition, when compared to non-*BRCA* mutation carriers who were age and tumor matched, patients who were *BRCA* mutation carriers were significantly more likely to have round, circumscribed, or rim-enhancing tumors (32).

Of note, although patients who are *BRCA1* mutation carriers and those who are *BRCA2* mutation carriers may develop cancers with seemingly benign morphology, several authors have reported that *BRCA1* mutation carriers tend to develop seemingly benign cancers more frequently than do *BRCA2* mutation carriers

Figure 2. Failure to characterize disease in a 63-year-old woman who presented for routine surveillance MRI, with a history of right breast triple-negative invasive ductal carcinoma 3 years previously who underwent breast conservation therapy. (a) Axial (left) and sagittal (right) T1-weighted fat-saturated postcontrast subtraction MR images show a 4-mm focus of enhancement (arrows) in the lumpectomy bed, thought to represent BPE. (b, c) Axial short τ inversion-recovery (STIR) MR image (b) shows a corresponding area of T2 hypointensity (arrow in b). However, this focus (arrow in c) is clearly dominant in comparison with foci depicted elsewhere in the breast, which is better appreciated on the axial MIP image (c), and its location in the region of the lumpectomy bed is suspicious. A 6-month follow-up MRI was recommended. (d) Axial (left) and sagittal (right) T1-weighted fat-saturated postcontrast subtraction MR images obtained 6 months later show that the focus (arrows) has increased in size and is now an 8-mm irregular mass. (e) Axial MIP image demonstrates the discrete mass (arrow). The results of a biopsy confirmed recurrent triple-negative breast cancer. Any dominant focus that appears to be different from the remaining scattered foci depicted elsewhere should raise suspicion for malignancy.

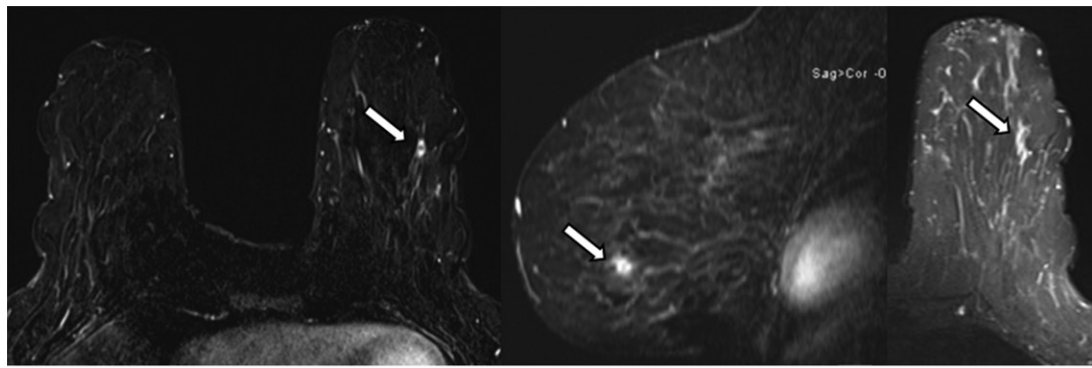


(33–35). In a study assessing the imaging phenotypes of breast cancers in women at moderate risk, at high familial risk, and who are *BRCA1* and *BRCA2* mutation carriers, Schrading et al (33) reported that 15 of 64 (23%) invasive cancers identified had a benign imaging appearance, appearing as fibroadenoma-like masses morphologically but without typical internal enhancement or kinetic patterns of fibroadenomas. Of these 15 cancers with seemingly benign features, seven (46.7%) were identified in patients with a confirmed *BRCA1* mutation, with an additional five (33.3%) identified in patients suspected but not confirmed to have a *BRCA1* mutation. Only one of 15 cancers with seemingly benign features was found in a patient with a *BRCA2* mutation (33).

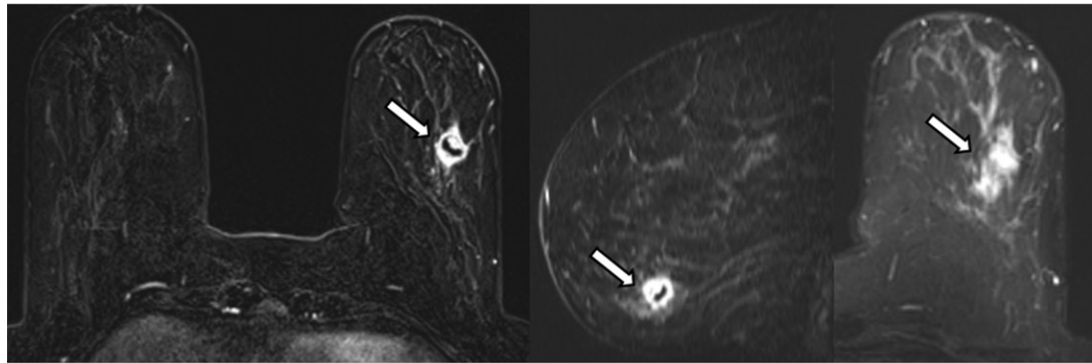
Similar findings were reported by Kuhl et al (34) in their study of MRI screening in patients with proven or suspected breast cancer susceptibility gene. The authors reported that five of 15 cancers detected demonstrated a round or ovoid shape, and four of five of these fibroadenoma-like cancers occurred in patients with the *BRCA1* gene

(34). These findings were further confirmed in a study by Ha et al (35), who reported the differences in imaging phenotypes between *BRCA1* and *BRCA2* mutation carriers. The authors reported that *BRCA1* mutation carriers were significantly more likely to develop cancers with circumscribed margins or rim enhancement than were *BRCA2* mutation carriers (35).

Furthermore, some cancers may change morphology over the course of imaging examinations, initially demonstrating more benign-appearing features before subsequently developing more suspicious imaging features. In a study by Gilbert et al (15) of patients with an inherited mutation or those at high risk with a strong family history of breast or ovarian cancer undergoing multiple rounds of screening MRI, of the 18 incident cancers (cancers not detected on the first round of screening), 66.7% of cancers were visualized on prior MR images, but their features were not diagnostic of malignancy at that time. In these cases, although the cancers were visualized retrospectively on the prior MR images, the lesions

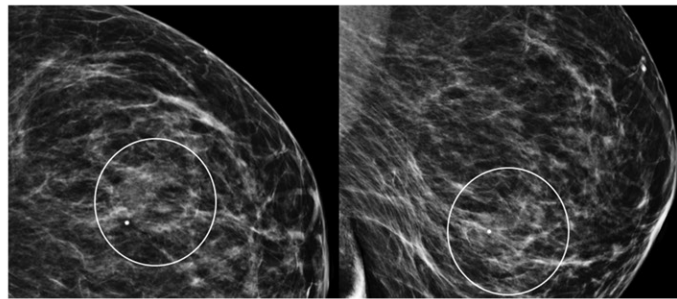


a.

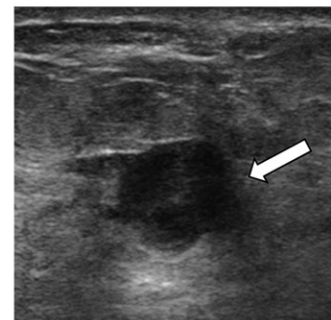


b.

Figure 3. Failure to characterize disease in a 51-year-old woman who presented for baseline high-risk screening MRI. Further additional information regarding the patient's risk factors was not available. **(a)** Axial (left) and sagittal (middle) T1-weighted post-contrast fat-suppressed subtraction MR images show an oval enhancing mass (arrows) in the lower outer quadrant, which was thought to be T2 hyperintense on the axial STIR image (right). As this was characterized as a probable fibroadenoma, 6-month follow-up MRI was recommended. **(b)** Axial (left) and sagittal (middle) T1-weighted post-contrast fat-suppressed subtraction MR images obtained 7 months later show the mass (arrows) is now rim enhancing with a mural nodule and was noted to have T2 hyperintensity centrally on the axial STIR image (right), representing central necrosis. Diagnostic mammography and US were recommended. At the time of diagnostic mammography and US, the patient stated that she had a palpable mass in the same location and that she is a known *BRCA1* mutation carrier. **(c)** Electronically magnified CC (left) and MLO (right) mammograms show a mass (circles) deep to the BB marker. **(d)** US image shows an irregular hypoechoic mass (arrow) with angular margins. The results of a biopsy confirmed triple-negative invasive ductal carcinoma. As *BRCA* mutation carriers may develop cancers with seemingly benign features, radiologists should have a low threshold for recommending biopsy in this population.



c.



d.

may have demonstrated seemingly benign features (such as being round in shape or having well-defined morphology) or may not have been easily visualized owing to their relatively smaller size. Although most of these lesions, in retrospect, had suspicious features at the prior examination, three of 12 cancers appeared well defined on the prior MR images when viewed in retrospect and subsequently became poorly defined in appearance, developing irregular margins or contours (15).

Similarly, although the presence of smooth margins of a mass has been reported as the most predictive feature of benignity (3), Liberman et al (36) reported that 17% of masses with smooth margins were malignant in their study of high-risk patients with masses detected at MRI. This finding is in contrast to that at mammography, for which the authors cited that smooth margins are associated with a 2% likelihood of

cancer (36). As such, radiologists should have a low index of suspicion to recommend biopsy in high-risk patients, as these patients may develop cancers with seemingly benign features.

Several theories have been proposed regarding the increased prevalence of malignancy of MRI-detected lesions with smooth margins (36). In women at high risk, including those who are *BRCA* mutation carriers, cancers may grow at a faster rate with a significantly shorter doubling time compared with cancers in women at average risk (37). As such, these cancers may grow so fast that they do not induce the desmoplastic reaction in the surrounding tissue caused by other slower-growing cancers, which results in an irregular or spiculated appearance at imaging. Furthermore, margin perception at MRI is based on technical factors such as spatial resolution and window or level settings, which may account for some of the differences in cancer appearances at MRI as compared with those at mammography and US (36). Finally, with anatomic-based imaging modalities such as mammography and US, margin perception is based on the appearance of the lesion as it interfaces with adjacent breast parenchyma. This is in contrast to MRI, in which lesion perception is based on the differences in vascularity and blood flow to a certain area compared with those of the adjacent tissue (36).

Although lesions may be more easily distinguished with postcontrast or subtraction sequences, review of other standard imaging sequences, most notably on T1-weighted non-fat-suppressed images, may be helpful once a lesion is identified. Lesion borders and morphology may be easier to assess on T1-weighted non-fat-suppressed images, which may aid in their accurate characterization. However, despite this, radiologists must be careful not to carry internal biases on the basis of tenets of typically benign features, developed from interpreting mammography and US examinations, that do not necessarily hold true for MRI (36).

False-Negative Results Due to Perceived Benign Kinetics

Just as the shape or margins of a mass may falsely dissuade a radiologist from deeming a lesion suspicious, some kinetic enhancement patterns commonly associated with a benign cause, such as a type 1 (persistent) enhancement pattern or the presence of dark internal septa (30), may also be found in the setting of malignancy. In a study by Gilbert et al (15) of cancers detected at screening MRI, of the 12 cancers that were not visualized on MR images prospectively but determined to have been visible retrospec-

tively, seven of 12 cases (58.3%) demonstrated a type 1 enhancement curve, in which the lesion demonstrates continuous contrast enhancement over time (15). A type 1 enhancement pattern is less frequently associated with malignancy than a type 2 pattern (ie, a plateau pattern, in which there is flattening of the enhancement curve following initial contrast material uptake) or a type 3 pattern (ie, washout pattern, in which there is rapid contrast material uptake followed by rapid washout) (30). However, in a multicenter study by Schnall et al (3), a type 1 enhancement pattern was found in 45% of lesions that turned out to be malignant (38).

Because some small invasive cancers as well as ductal carcinoma in situ (DCIS) do not demonstrate the type 3 (washout) pattern found in larger invasive cancers, radiologists should not rely solely on enhancement kinetics when characterizing lesions (12,39–42). For example, Zuiani et al (39) studied the MRI features of 28 cases of DCIS and reported that although most DCIS lesions did show contrast enhancement (26 of 28 lesions [92.3%]), a type 1 enhancement curve was found in four of 26 DCIS lesions (15.4%), including three of 17 (17.6%) pure DCIS lesions and one of nine (11.1%) cases of DCIS with microinvasion.

Similarly, Scott-Moncrieff et al (40) evaluated the MRI features of noncalcified versus calcified DCIS lesions in their study of 115 cases of pure DCIS lesions. The authors reported no significant difference in the delayed enhancement patterns of calcified versus noncalcified DCIS. However, the authors reported that DCIS lesions demonstrated a persistent delayed enhancement pattern in nearly half of cases (36 of 64 noncalcified DCIS lesions [56%]; 24 of 50 calcified lesions [48%]). The authors also noted that two of 50 (4%) calcified DCIS lesions demonstrated enhancement below the threshold for detection and instead were only visualized at mammography (40). These findings were supported by Jansen et al (41) in a study of 79 cases of pure DCIS, for which the authors reported all patterns of delayed enhancement, noting that 30% of lesions (24 of 79) demonstrated a persistent delayed enhancement pattern, while 25% (20 of 79) demonstrated a plateau delayed enhancement pattern (41).

Some invasive cancers may not demonstrate washout kinetics at MRI, particularly small invasive cancers (12,42). Meissnitzer et al (42) assessed the MRI features of invasive cancers of a range of histologic sizes. The authors reported that benign characteristics were present in many invasive breast cancers that were less than or equal to 5 mm in size. They also reported that there was a significant difference in the delayed kinetic enhancement pattern of invasive cancers

at MRI on the basis of lesion size, with the largest proportion of cancers demonstrating persistent enhancement in the less than or equal to 5 mm category (11 of 27 lesions [41%]), with that proportion decreasing with increased size. The authors reported that 29% of lesions less than 15 mm demonstrated persistent enhancement (29 of 101 lesions, which ranged from >5 mm to ≤10 mm in size; five of 17 lesions, which ranged from >10 mm to ≤15 mm in size). For lesions greater than 15 mm in size at MRI, only one cancer of six (17%) demonstrated persistent enhancement (42).

Just as patients with a *BRCA* mutation may develop cancers with a seemingly benign morphology, they may also develop cancers with less suspicious kinetic enhancement patterns (33,35). In a study of the MRI features of familial breast cancers (which included women with an elevated lifetime risk of cancer, with and without the *BRCA1* or *BRCA2* mutation gene), Schrading et al (33) reported that 25 of the 76 cancers (including both invasive and in situ cancers) demonstrated more typically benign kinetic enhancement patterns, as evidenced by a slow early rise followed by persistent delayed enhancement. The authors noted that this was discrepant when compared with kinetic enhancement patterns reported in their earlier studies of women in the general population who did not have a history of familial breast cancer, in whom a type 1 enhancement pattern was visualized in only 8.9% (nine of 101) of cancers (43).

Ha et al (35) also reported that although the patterns of delayed enhancement did not differ significantly between *BRCA1* and *BRCA2* mutation carriers, both populations developed cancers with either type 1 or type 2 enhancement patterns. The authors found that two of 97 (2.1%) cancers in *BRCA1* mutation carriers and four of 102 (3.9%) cancers in *BRCA2* mutation carriers demonstrated persistent delayed enhancement, while nine of 97 (9.3%) cancers in *BRCA2* mutation carriers and 11 of 102 (10.8%) cancers in *BRCA2* mutation carriers demonstrated plateau delayed enhancement (35).

Masses that demonstrate nonenhancing (dark) internal septa, a pattern often associated with fibroadenomas (44,45), have also served as a potential pitfall in falsely suggesting benignity (11,23). In a study by Pages et al (11), 15 of 60 lesions were correctly identified at prior MRI but were falsely interpreted as benign lesions, four of which were misinterpreted owing to masses with nonenhancing internal septa incorrectly characterized as fibroadenomas. In three of four cases (75%), the radiologist was falsely swayed because the patients had known fibroadenomas (11).

Similar findings were reported in a study by Wurdinger et al (23), in which two false-negative

diagnoses were secondary to mischaracterization of masses perceived to be fibroadenomas because of nonenhancing internal septa. However, the authors noted that, retrospectively, these lesions demonstrated suspicious enhancement patterns, with rapid contrast material uptake followed by washout, which should have swayed the radiologist to consider a more suspicious cause (23). As such, radiologists should exercise caution when characterizing a mass with nonenhancing internal septa as a fibroadenoma unless it is in conjunction with other benign features characteristic of fibroadenomas, such as round or ovoid shape, circumscribed margins, or T2 hyperintensity.

Given that no single imaging characteristic alone at MRI can confirm a benign cause, radiologists should carefully consider all attributes of a mass when characterizing lesions. Shape, margins, and enhancement kinetics, along with a patient's clinical history and risk factors, should all be considered when attributing a benign or suspicious morphology. The presence of any suspicious features, even in the setting of other seemingly benign characteristics, should sway a radiologist toward recommending tissue sampling.

Cancers Detected in the BI-RADS Category 3 (Probably Benign) Population

Despite some cancers having seemingly benign features at MRI, it is reasonable at times to recommend short-interval follow-up (BI-RADS category 3) in lieu of biopsy (BI-RADS category 4) for lesions that the radiologist thinks have a low chance of malignancy. Per the BI-RADS Atlas, mammographic lesions assigned a BI-RADS category 3 should have a less than 2% chance of malignancy (46). However, for MRI BI-RADS category 3 assessments, although lesions should have a high probability of being benign, there is no defined expected rate of malignancy (47–50).

Several studies have explored the rate of malignancy in BI-RADS category 3 lesions. In a meta-analysis of 15 studies assessing the prevalence and malignancy rates of BI-RADS category 3 lesions, Spick et al (47) reported malignancy rates ranging from 0.5% to 10.1% (47–49), with a pooled malignancy rate of 1.6% (61 of 2814 lesions) (47). In a subgroup analysis, they reported that the rate of malignancy was highest for nonmass enhancement (25 of 714 lesions, pooled by random effects model: 2.3%), followed by masses (15 of 771 lesions, pooled by random effects model: 1.5%). Foci had the lowest pooled rate of malignancy, with an overall 1.0% (10 of 698 lesions) (47).

However, although cancers have been reported in the BI-RADS category 3 population, some studies have reported that cancers diagnosed in this subgroup tend to be early stage (50). In a

study of 6672 breast MRI screening examinations, Edmonds et al (50) reported an overall 3% BI-RADS category 3 assessment (202 of 6672), with a 6% rate of malignancy among BI-RADS category 3 lesions (13 of 202). However, 12 of 13 cancers (92.3%) were stage 0 or stage 1 node-negative breast cancers. The authors acknowledged that, although the 6% rate of malignancy is higher than the generally accepted less than 2% rate for mammographic and US BI-RADS category 3 lesions, the patients in their study are at a higher risk than the general population for developing breast cancer and, as such, a higher rate of malignancy in this BI-RADS category 3 subpopulation is not surprising (50).

Pearls and Pitfalls of T2-weighted Sequences

T2-weighted imaging, in conjunction with post-contrast imaging, has been used to characterize masses at MRI. Frequently, high signal intensity at T2-weighted imaging that corresponds with the enhancing portion of a mass is highly suggestive of a benign cause (38). Most breast cancers are T2 hypointense or isointense owing to their dense cellularity (38,51). However, T2-weighted images must be interpreted with extreme caution, as some malignancies may be T2 hyperintense. T2 hyperintensity must only be used as a criterion for attributing a benign cause when it is also associated with other benign imaging features, including benign morphology. A suspicious morphology, such as an irregular or spiculated mass, should always prompt the recommendation to perform biopsy, regardless of the T2 characteristics (38).

However, even then, extreme caution should be used when relying on T2 signal intensity, as several carcinoma subtypes including mucinous, apocrine, papillary, medullary, and anaplastic cancers may be T2 hyperintense. Some of these subtypes (most commonly mucinous carcinomas) are commonly round or ovoid in shape. Centrally necrotic tumors may also have large T2-hyperintense components (51). As such, when interpreting the T2-weighted images, it is critical to ensure that the T2-hyperintense component directly corresponds to the enhancing component of the mass. In the case of centrally necrotic tumors, there may be a peripheral rim of viable enhancing tissue surrounding a large amount of central necrosis appearing as a rim-enhancing mass on MR images. Although rim enhancement represents a suspicious enhancement pattern, radiologists could be fooled by the apparent T2-weighted hyperintensity of the mass, without realizing that the T2 hyperintensity actually corresponds to the centrally necrotic nonviable tissue component of the mass, resulting in a missed cancer diagnosis.

Similar to the characterization of masses, caution must be exercised when using T2 hyperintensity to characterize nonmass enhancement at MRI. In a study by Chikarmane et al (52) of the analysis and outcomes of nonmass enhancement rated as BI-RADS category 3, 4, or 5, malignant nonmass enhancement was T2 hyperintense in 32% of cases (17 of 52), including both ductal carcinoma in situ (9 of 17 cases [53%]) and invasive carcinoma (8 of 17 cases [47%]). The authors reported that the T2 hyperintensity depicted in association with malignant nonmass enhancement may be due to edema, necrosis, or lymphatic invasion. As such, radiologists should not rely on T2 hyperintensity to suggest a benign cause for nonmass enhancement, particularly if associated with a more suspicious internal enhancement pattern such as a heterogeneous, clumped, or clustered ring (52).

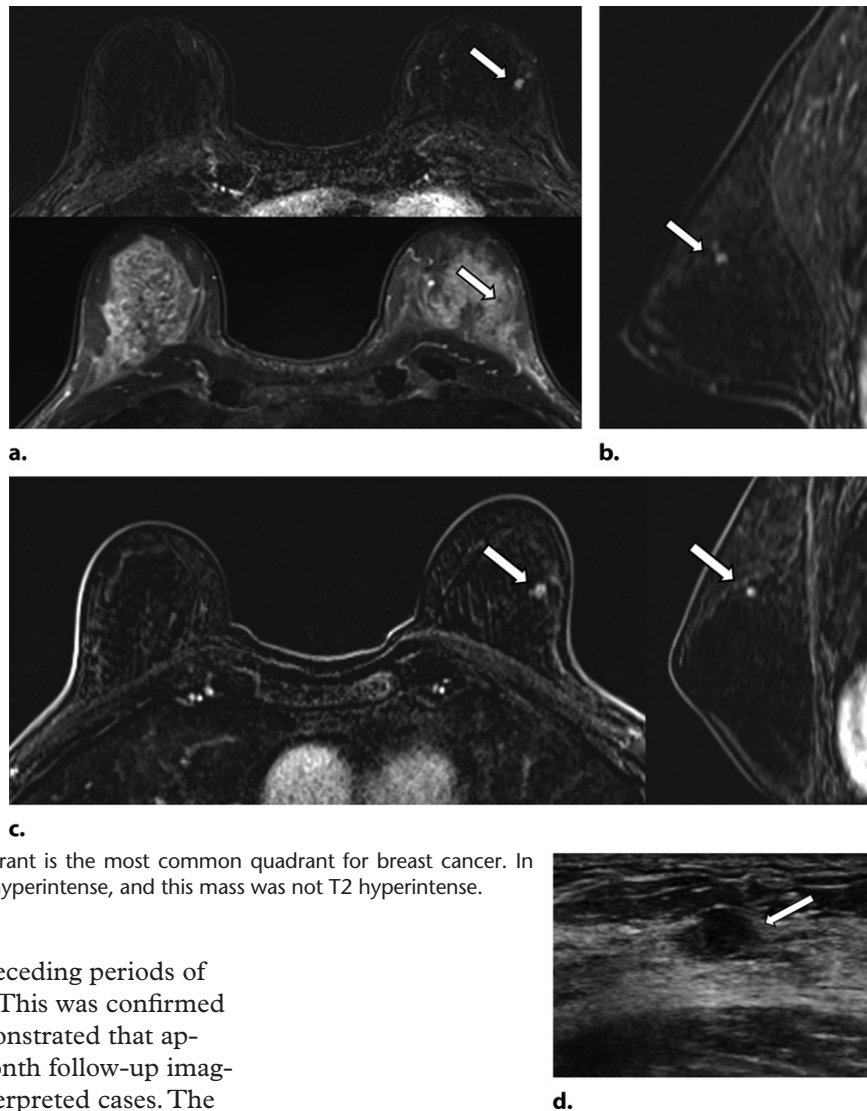
Similarly, T2-weighted images are often used to classify small ovoid or round masses at MRI as lymph nodes, particularly when they occur in the upper outer quadrant of the breast, as intramammary lymph nodes may be frequently found in this location. However, a small T2-hyperintense enhancing mass in the upper outer quadrant of the breast cannot be characterized as a lymph node on the basis of its location alone, as breast cancers may also occur in this location (Fig 4). Identification of other characteristic features of a lymph node such as a fatty hilum may be helpful, with the realization that these may be difficult to appreciate at MRI owing to volume averaging. Radiologists must apply the same standards when evaluating masses in the upper outer quadrant as elsewhere in the breast and should not simply attribute an enhancing mass in this location as a lymph node, regardless of the T2-weighted signal intensity.

Failure to Characterize a “Stable” Finding

Long-term stability of findings is often suggestive of a benign cause. However, several studies have reported that cognitive errors in interpreting lesion stability have resulted in false-negative findings (1,11,12,16) (Fig 5). In a study by Maxwell et al (12), there were three false-negative MRI examination results in which nonmass enhancement was retrospectively visualized on the prior images. In two-thirds of these cases (66.6%), the nonmass enhancement was either stable or only slowly enlarging (12). Similarly, in the MARIBS study, two of the 12 misinterpreted breast cancers were stable in size at two consecutive screening MRI examinations (11).

Differences in tumor biology and growth patterns may be to blame for seemingly stable findings resulting in missed breast cancers. Some tumors may have variable growth patterns, with

Figure 4. Failure to characterize disease in a 65-year-old woman with prior negative “heterogeneously dense” mammogram results who presented for supplemental MRI screening. (a) Axial (top) T1-weighted postcontrast fat-suppressed subtraction and axial STIR (bottom) MR images show a round enhancing mass (arrows) in the upper outer quadrant, noted to have low signal intensity on T2-weighted images. (b) Sagittal T1-weighted postcontrast fat-suppressed subtraction MR image also shows the mass (arrow), which was thought to represent an intramammary lymph node. A 6-month follow-up was recommended. (c) Axial (left) and sagittal (right) T1-weighted postcontrast fat-suppressed MR images obtained 6 months later show that the mass (arrows) has increased in size. (d) Second-look US image shows an oval hypoechoic mass (arrow) with irregular margins. Biopsy results confirmed invasive ductal carcinoma with DCIS. The radiologist should not assume that a small round enhancing mass in the upper outer quadrant is a lymph node on the basis of location alone, as the upper outer quadrant is the most common quadrant for breast cancer. In addition, lymph nodes are often T2 hyperintense, and this mass was not T2 hyperintense.



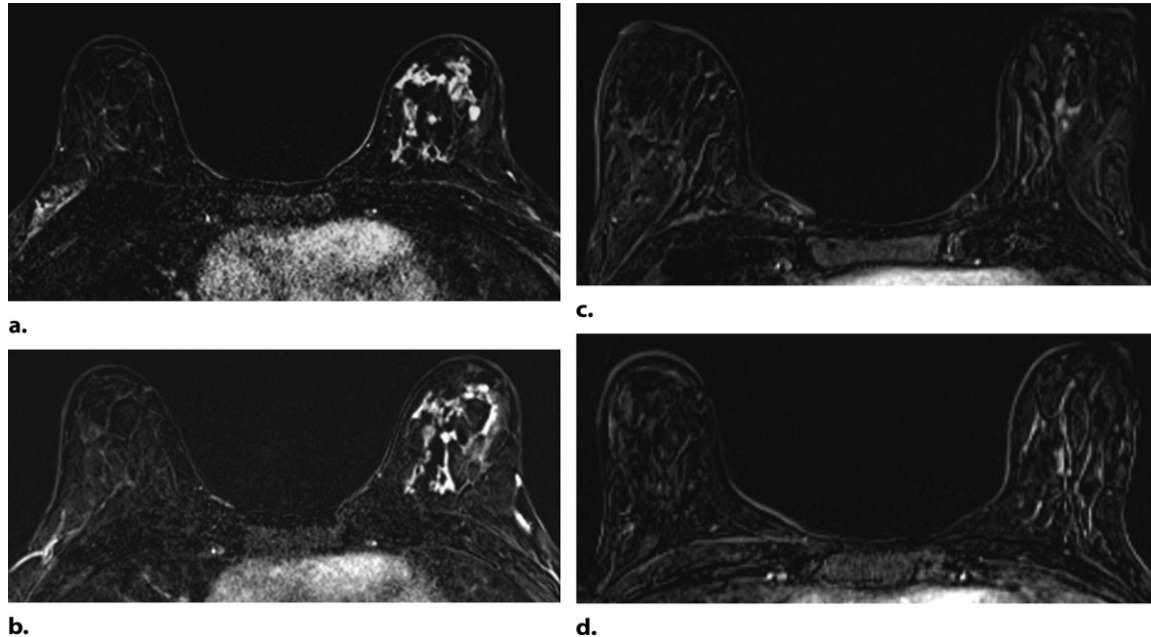
relative periods of stability preceding periods of rapidly increased growth (1). This was confirmed by Pages et al (11), who demonstrated that apparent lesion stability at 6-month follow-up imaging resulted in 20% of misinterpreted cases. The authors proposed that this phenomenon is found more often in older patients, whereas higher-risk younger patients often develop tumors with a more rapid doubling time (11).

Similar findings were observed in patients with the *BRCA* mutation. In a study by Tilanus-Linthorst et al (37) of breast cancer tumor doubling times, the authors reported that patients with either the *BRCA1* or *BRCA2* mutation had a tumor doubling time twice as fast as that in other high-risk women of the same age but noted no difference in tumor doubling times between patients with the *BRCA1* versus *BRCA2* mutation. The authors noted that increasing age was associated with a decreased growth rate, for patients with the *BRCA* mutation as well as for high-risk patients. For example, the authors reported that for patients with the *BRCA* mutation, tumor doubling time was 1 month for patients younger than 40 years, 2 months for patients between ages 41–50 years, and 3 months for those patients diagnosed after 50 years of age (corresponding doubling time for high-risk patients without the

BRCA gene were 3 months, 4 months, and 6 months, respectively) (37). These differences in tumor biology resulting in differences in tumor growth rate were confirmed on a microscopic level in another study by Tilanus-Linthorst et al (53), who reported that patients with the *BRCA1* or *BRCA2* mutation had higher mitotic rates than sporadic cancers diagnosed in patients who were matched for age and year of diagnosis.

Given that breast cancers may appear stable between examinations, it is critical that the radiologist use all available prior comparison examinations when attempting to confirm relative stability of a lesion. Rather than reviewing only the most recent comparison prior examination, it is helpful to begin by first reviewing either the most remote prior examination or an examination from several years prior. The radiologist can then review the sequentially obtained prior examinations until reaching the most recent comparison examination when assessing for the stability of a finding. In this

Figure 5. Failure to characterize disease in a 36-year-old woman who is a *BRCA2* mutation carrier and presented for screening MRI. Axial T1-weighted postcontrast fat-saturated subtraction MR images obtained most recently (a) and 1 year (b), 2 years (c), and 3 years (d) earlier show clumped regional nonmass enhancement in the left breast, asymmetric to the right breast, on the most recently obtained MR image (a). The finding was erroneously noted to be stable compared with that on the previous image (b). On the MR image obtained the previous year (b), the nonmass enhancement was described as a “physiologic variant of BPE” owing to the results of same-day normal mammography and US (not shown) and clinical breast examination. The nonmass enhancement was recommended for biopsy the following year after screening (not shown), and the pathologic results confirmed extensive high-grade DCIS. When reviewing prior examinations to assess for stability, it is important to compare all the available prior examinations, particularly those that are more remote, on which a distinct change over time may be more easily appreciated. Changes over time may not be apparent when comparing with only the most recent previous examination, and malignant findings may appear seemingly stable between examinations.



way, the radiologist can more easily appreciate distinct changes in appearance over time.

Missed Cancers in the Postsurgical Breast

MRI examinations of the postsurgical breast can be challenging to interpret owing to altered anatomy, as well as the potential for confounding diagnoses such as fat necrosis. Several studies have reported small foci or nonmass enhancement in the area surrounding or abutting the lumpectomy bed, mimicking postoperative change, as a cause for false negatives (4,11) (Fig 6). Most commonly, this has occurred when the radiologist confuses enhancement in the lumpectomy bed as secondary to normal evolving postoperative changes, such as fat necrosis. Expected postsurgical MRI findings following breast conservation therapy may include architectural distortion, improving edema, and postoperative seroma with a thin uniform rim of enhancement (<5 mm) (54). However, any masslike or nodular areas of nonmass enhancement surrounding a postsurgical seroma should be considered as suspicious (54). The radiologist should pay careful attention when characterizing enhancement in the area surrounding or abutting the surgical bed, and any change in the enhancement pattern

should be regarded with a high index of suspicion, as this is the most common site for recurrent disease (55,56). If abnormal enhancement is identified that is thought to represent fat necrosis, correlation with T1-weighted non-fat-suppressed images may be helpful to confirm the presence of intralesional fat. Edema should improve over time, and increasing edema after breast conservation therapy may be a manifestation of recurrent disease (54). Careful correlation with the patient's operative history must also be considered. Although postsurgical findings such as fat necrosis may evolve over several years, a change in appearance of the lumpectomy bed remote from surgery should prompt concern.

Similarly, the radiologist should carefully evaluate the reconstructed breast in a patient who has undergone mastectomy and who is undergoing MRI, as small local recurrences may occur (Fig 7). Following mastectomy, some patients choose to undergo either implant-based or myocutaneous flap reconstruction. Of the myocutaneous flap reconstruction options, transverse rectus abdominis myocutaneous (TRAM) flap reconstruction is the most commonly performed, which is associated with a low (2%–4%) but not zero risk of local recurrence (57,58). Most locally recurrent breast

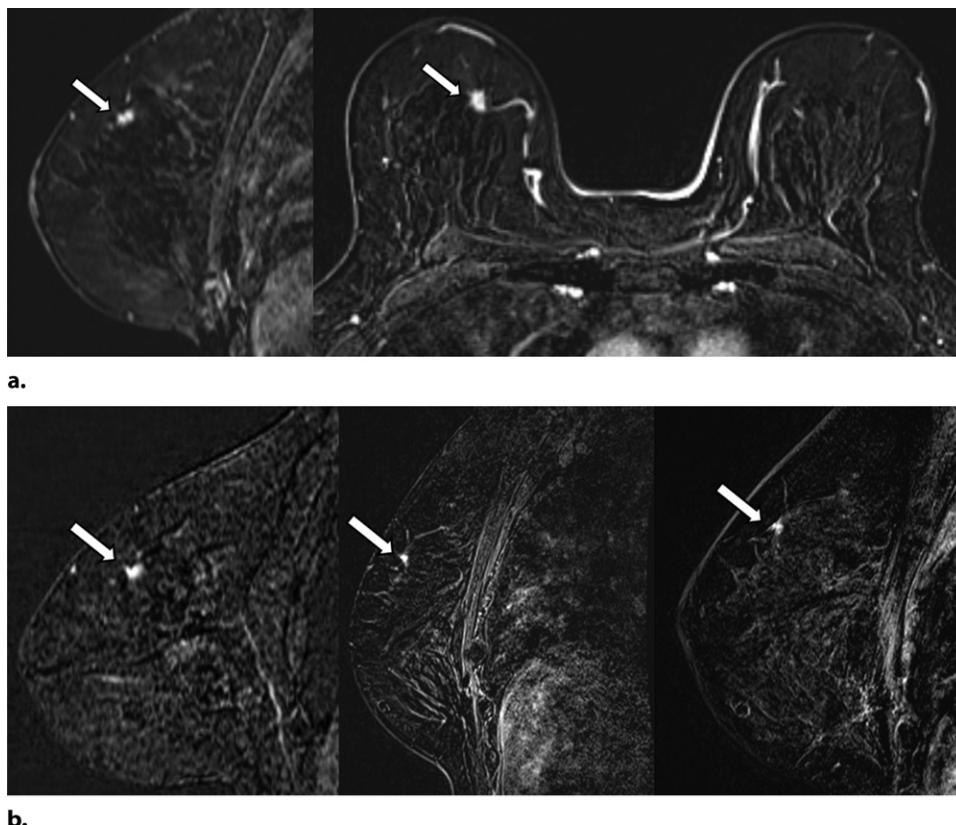


Figure 6. Failure to detect disease in a 52-year-old woman undergoing MRI surveillance after breast conservation therapy 9 years earlier. **(a)** Sagittal (left) and axial (right) T1-weighted postcontrast fat-suppressed subtraction MR images show a 6-mm irregular mass (arrows) in the upper central breast in the lumpectomy bed, which was recommended for MRI-guided biopsy. The pathologic test results confirmed recurrent invasive ductal carcinoma. **(b)** However, in retrospect, this irregular mass (arrows) has been visible and slowly growing when compared to prior surveillance MR images, as depicted on sagittal T1-weighted postcontrast fat-suppressed subtraction MR images obtained 1 year (left), 2 years (middle), and 3 years (right) earlier. Enhancement in the surgical bed remote from surgery should raise suspicion, as postoperative changes such as fat necrosis are not expected to occur many years after surgery. The radiologist should pay extra attention to the lumpectomy bed, as this is the most common site of in-breast recurrence.

cancers in patients who have undergone flap reconstruction occur in either the skin or subcutaneous tissues and most often manifest as clinically palpable masses (57).

However, an increasing number of patients who have undergone a unilateral mastectomy for breast cancer are undergoing supplemental screening with MRI of the contralateral native breast, which results in imaging of the reconstructed breast at the same time, as it is included in the field of view at MRI. When evaluating the flap reconstruction on MR images, radiologists must pay careful attention to the contact zone, the junction between the native residual breast tissue and the flap reconstruction, as this is a common site of recurrence (57,58). On MR images, this is most often depicted as a linear band that demonstrates low-to-intermediate signal intensity on T1-weighted images and that parallels the contour of the breast (57,59). However, the radiologist should be wary of any area of abnormal enhancement along the contact zone,

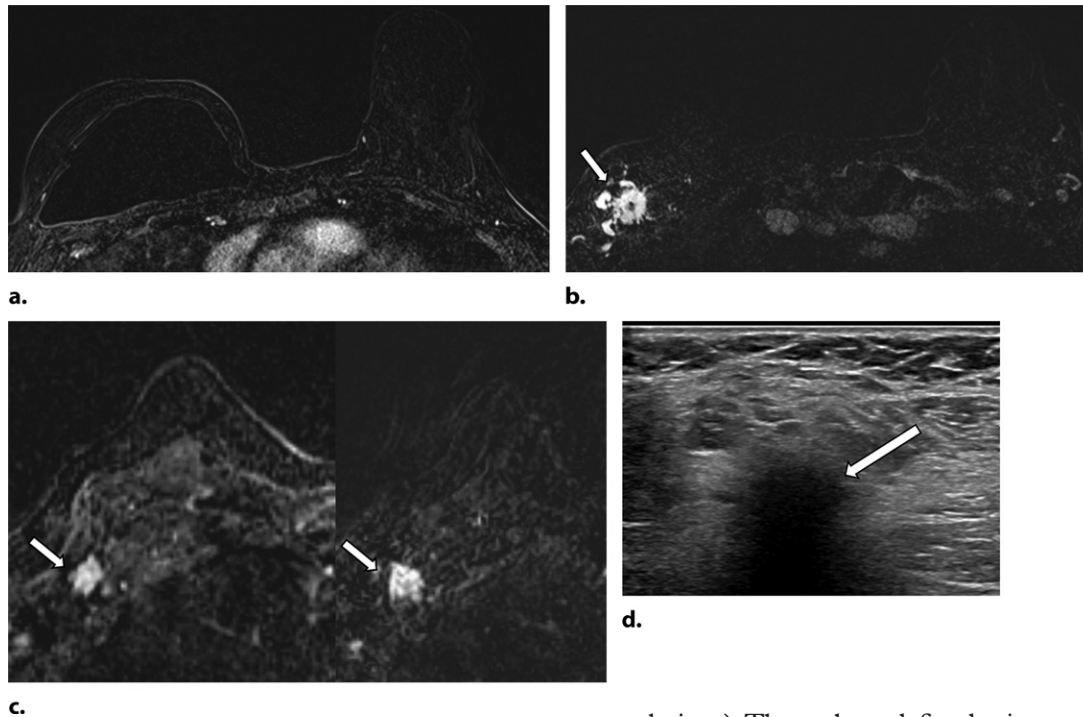
particularly if it lacks features consistent with fat necrosis, as this area represents a common potential site of recurrent disease.

Poor Intermodality Correlation

When abnormal findings are identified at MRI and biopsy is recommended, MRI-directed US or mammography may be recommended. The purpose of the MRI-directed mammography and US is to identify a mammographic or US correlate for the abnormality depicted on the MR image, as MRI-directed biopsies have downsides, including patient discomfort with prone positioning, cost, and lack of real-time targeting confirmation. However, the radiologist should pay careful attention to ensure that a lesion identified at MRI-directed US does, in fact, correspond with the initial suspicious MRI finding that prompted the recommendation. Otherwise, false-negative cases may occur (Fig 8).

Several studies have assessed both the likelihood of detection and the outcomes of MRI-directed US. The imaging findings associated with

Figure 7. Failure to detect disease in a 73-year-old woman who underwent right mastectomy for breast cancer and who presented for MRI surveillance of the left breast. (a–c) Axial T1-weighted postcontrast fat-suppressed subtraction MR images obtained at different levels (a, b) show no suspicious findings in the left breast in a (representative image). However, there is an irregular spiculated mass in the right axilla in b (arrow in b). In retrospect, it can be visualized that this mass (arrows in c) has been visible and slowly enlarging when compared with findings on the axial T1-weighted postcontrast fat-suppressed subtraction MR images obtained 1 year (left image in c) and 2 years (right image in c) earlier. The abnormality was simply not visualized, likely because the radiologist had focused their attention on screening the contralateral breast and ignored the right reconstructed breast following mastectomy. (d) Second-look US image shows an irregular hypoechoic mass. The results of a biopsy confirmed recurrent invasive breast cancer replacing an axillary node. When interpreting every examination, it is important to develop a thorough search pattern, including an evaluation of the axillae and extramammary sites (including the mediastinum, lungs, liver, and bones) to avoid missing potential sites of disease.



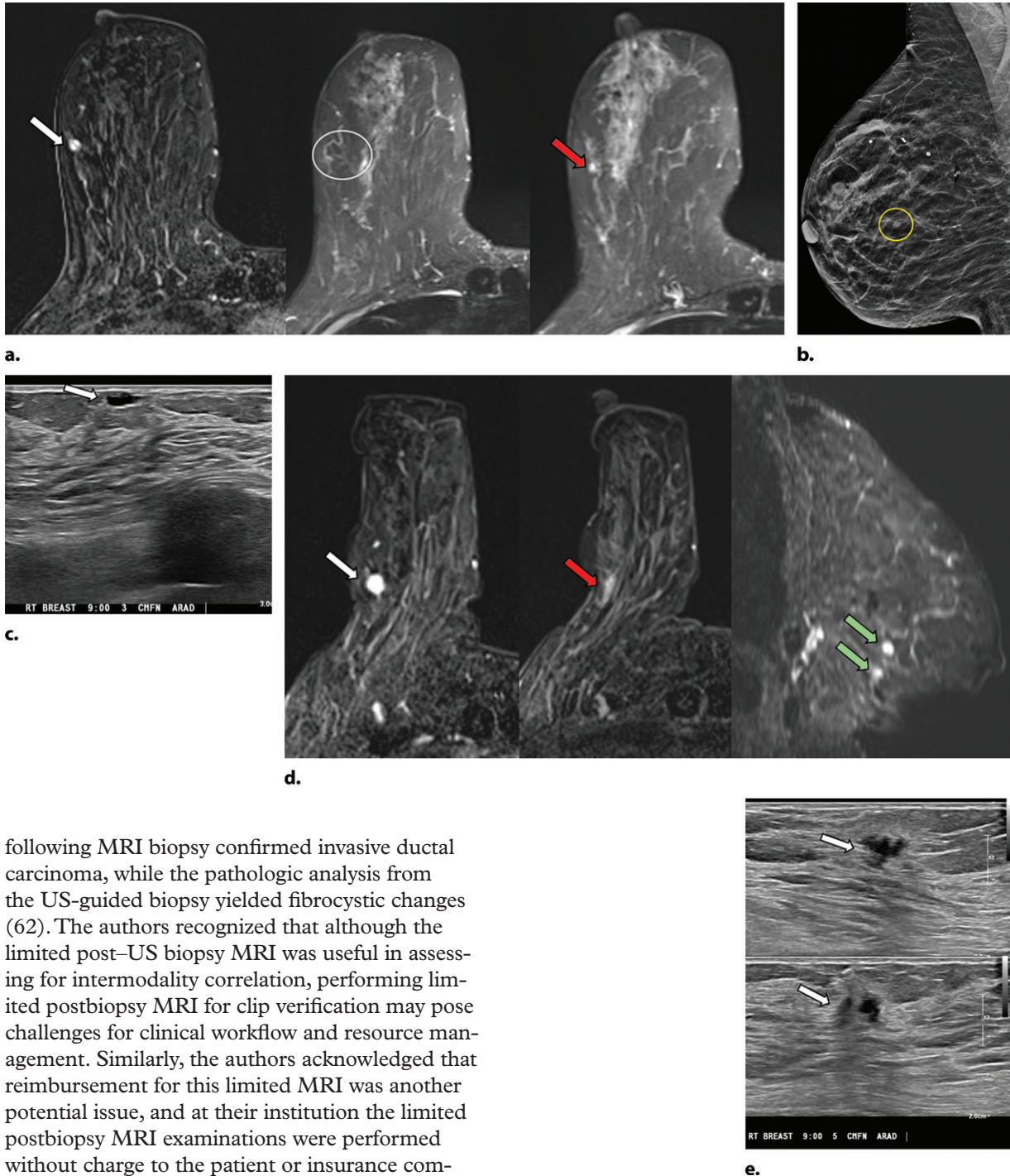
an increased likelihood of identification at MRI-directed US include masses (followed by nonmass enhancement, then foci), increased size of a finding, and malignant pathologic findings following biopsy (60,61). In some of the larger-scale studies of MRI-directed US, detection rates of presumed US correlates were similar. Meissnitzer et al (61) reported a presumed correlate 56% of the time (290 of 519 lesions) (61), and Chikarmane et al (60) reported that US correlates were found in 57% of cases (298 of 522 lesions) (60). However, both studies reported that incorrect US–MRI correlation did occur. Meissnitzer et al (61) reported that the US finding did not correspond to the MRI finding in 10 of 80 benign concordant US biopsies, and five of nine of these discordant lesions that ultimately proceeded to MRI biopsy demonstrated cancer (61). Similarly, Chikarmane et al (60) reported that US biopsy clip placement was inaccurate in 11 of 83 benign concordant biopsies (13%). However, only one cancer was ultimately diagnosed in this cohort (60).

Similarly, in a study by Pages et al (11), the authors attributed mismanaged enhancement as the cause of 12% of missed cancer cases (seven of 60

lesions). The authors defined *mismanaged enhancement* as enhancement that was correctly identified as suspicious at MRI that did not result in a cancer diagnosis following the results of a biopsy. The authors attributed the majority of mismanaged cases to inadequate MRI–US correlation, noting that in five of seven cases, biopsy was performed under US guidance for a presumed MRI correlate (11). Noting the differences in patient positioning between MRI and US by using anatomic landmarks such as relative depth in the breast or position at a fat–fibroglandular interface may help avoid incorrect intermodality correlation.

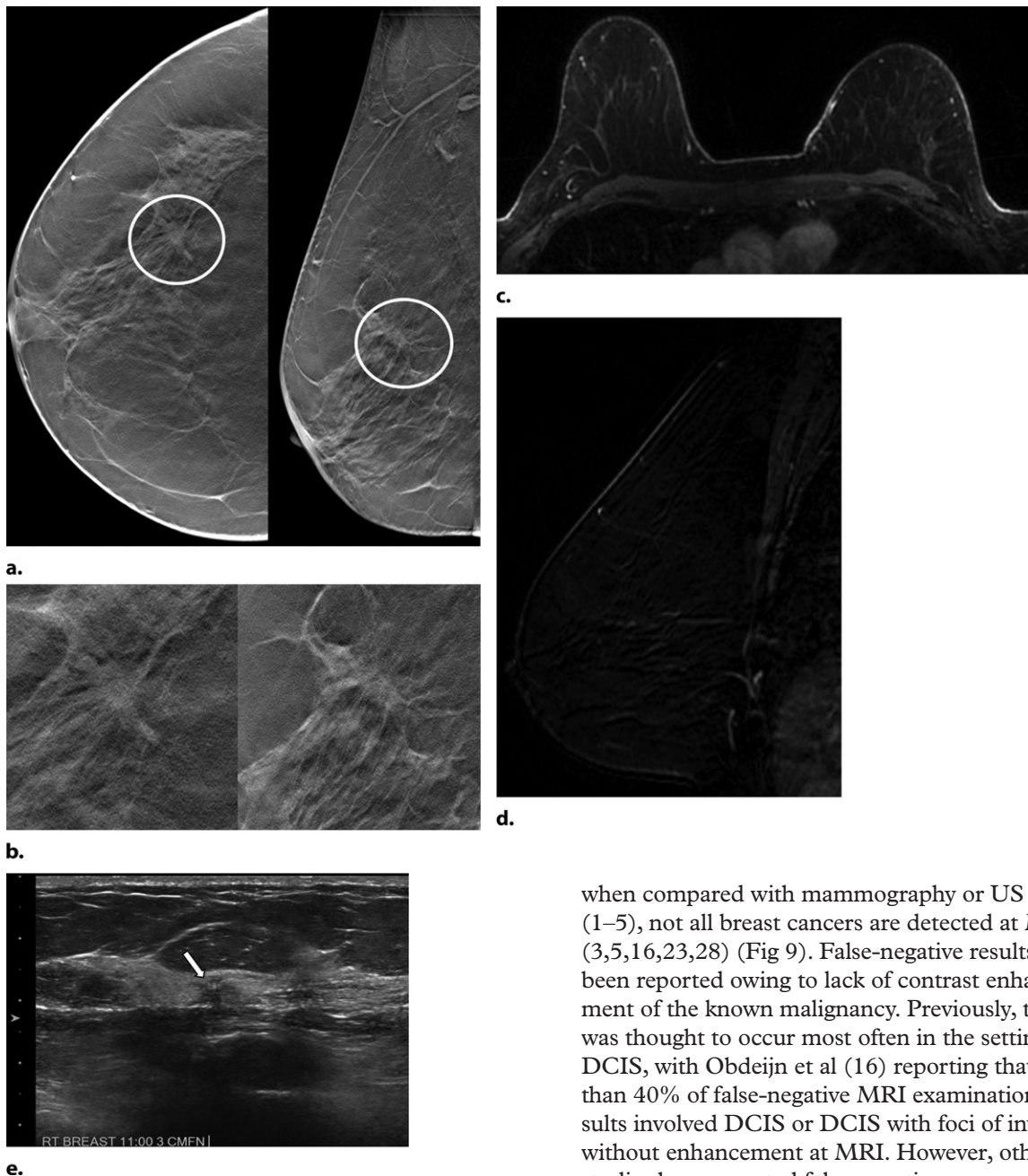
Some authors have proposed that a postbiopsy limited MRI (consisting of T1-weighted non-fat-saturated and T2-weighted fat-saturated sequences) could help assess for US–MRI correlation. In a study by Lee et al (62) of patients who underwent US-guided core biopsy of a presumed US correlate for a suspicious MRI finding and who also underwent postbiopsy limited MRI for clip verification, the authors reported that for 26% of lesions (10 of 38), the susceptibility artifact at MRI from the US-guided biopsy clip localized to a site remote from the suspicious MRI finding at the postbiopsy MRI. In one of these discordant cases (one of 10 [10%]), the pathologic analysis

Figure 8. Poor intermodality correlation in a 72-year-old woman undergoing surveillance MRI after a remote history of left breast conservation therapy. **(a)** Axial T1-weighted postcontrast fat-suppressed subtraction MR image (left) shows a round enhancing mass (white arrow) in the outer right breast. Co-localized axial STIR image (middle) shows no corresponding T2-hyperintense mass in this location (circle). However, there is a T2-hyperintense round mass (red arrow) that is slightly more inferiorly located in the outer breast on the axial STIR image (right), which does not correspond to the enhancing mass. Second-look mammography and US were recommended. **(b)** MLO mammogram shows an asymmetry (circle) in the outer right breast, depicted only on the MLO image. **(c)** US image shows a cyst (arrow), which was erroneously thought to correspond to the enhancing mass. At the time of diagnostic US, the T2-hyperintense mass in the outer breast (right image in **a**) was incorrectly thought to correspond to the enhancing mass (left image in **a**). Instead of biopsy, 6-month follow-up MRI was recommended. **(d)** Axial T1-weighted postcontrast fat-suppressed subtraction MR images (left and middle) show that the initial mass (white arrow) has grown, and an enhancing satellite mass (red arrow) is depicted inferiorly and medially. Both masses (green arrows) are depicted on the sagittal T1-weighted postcontrast fat-suppressed subtraction MR image (right). **(e)** Targeted US images show two adjacent irregular hypoechoic suspicious masses (arrows). Biopsy results confirmed invasive ductal carcinoma. Careful intermodality correlation is necessary to avoid attributing a benign unrelated mammographic or US finding as the cause of a suspicious MRI abnormality. If there is any doubt about intermodality correlation, MRI-directed biopsy should be performed.



following MRI biopsy confirmed invasive ductal carcinoma, while the pathologic analysis from the US-guided biopsy yielded fibrocystic changes (62). The authors recognized that although the limited post-US biopsy MRI was useful in assessing for intermodality correlation, performing limited postbiopsy MRI for clip verification may pose challenges for clinical workflow and resource management. Similarly, the authors acknowledged that reimbursement for this limited MRI was another potential issue, and at their institution the limited postbiopsy MRI examinations were performed without charge to the patient or insurance company. Given these factors, if there is doubt about

Figure 9. Cancer not visualized at MRI in a 56-year-old woman who presented for routine screening mammography. (a, b) CC (left) and MLO (right) mammograms (a) and electronically magnified CC (left) and MLO (right) mammograms (b) show architectural distortion in the upper central right breast, which persisted at callback evaluation (not shown). US (not shown) showed no suspicious findings. The radiologist recommended breast MRI instead of biopsy. (c, d) Axial (c) and sagittal (d) T1-weighted postcontrast fat-suppressed subtraction MR images show no suspicious enhancement in the upper central right breast. The patient returned the following year for mammography, with the architectural distortion in the right breast unchanged (not shown). (e) US image shows a subtle irregular hypoechoic mass (arrow). The results of a biopsy confirmed low-grade invasive ductal carcinoma. Some cancers, including DCIS, some invasive lobular carcinomas, and some other low-grade invasive tumors, may not demonstrate enhancement at MRI. As such, the radiologist should exercise extreme caution when recommending MRI instead of biopsy as a means for resolving suspicious mammographic or US findings, as false-negative cancers may occur.



a possible correlate at mammography or US, an MRI-directed biopsy should be recommended to ensure that the correct lesion is targeted.

Cancers Not Visualized on MR Images

Although MRI is the most sensitive single imaging modality for the detection of breast cancer

when compared with mammography or US alone (1–5), not all breast cancers are detected at MRI (3,5,16,23,28) (Fig 9). False-negative results have been reported owing to lack of contrast enhancement of the known malignancy. Previously, this was thought to occur most often in the setting of DCIS, with Obdeijn et al (16) reporting that more than 40% of false-negative MRI examination results involved DCIS or DCIS with foci of invasion, without enhancement at MRI. However, other studies have reported false-negative cases owing to nonenhancement of invasive cancers as well (3,5,23,28). In a study by Schnall et al (3), 16% of DCIS lesions and 3% of invasive carcinomas demonstrated no enhancement at MRI. Similar results were reported by Wurdinger et al (23) in their study of preoperative breast MRI performed in patients with 234 sequentially diagnosed breast cancers. The authors found that five of 193

invasive carcinomas (2.6%) and five of 41 DCIS lesions (12.2%) were not visualized at MRI owing to either delayed or no contrast enhancement (23).

Unlike mammography or US in which cancers are detected on the basis of anatomic abnormalities, MRI-detected cancers rely on altered tumor vascularity, resulting in differing contrast enhancement of the cancer compared with that of the surrounding parenchyma. Many breast cancers develop an increased capillary network and increased vascular permeability through their release of certain angiogenic factors, primarily vascular endothelial growth factor (VEGF), which induces both the proliferation of preexisting capillaries as well as the formation of new vessels. These factors contribute to their earlier and more intense contrast enhancement compared with that of normal fibroglandular tissue at MRI (5,63).

However, this pattern is not seen in association with all breast cancer subtypes, particularly invasive lobular carcinoma, certain well-differentiated invasive carcinomas (such as tubular carcinoma), or cirrhotic or desmoplastic types of invasive ductal carcinoma. In the case of invasive lobular carcinomas, angiogenesis is mediated through other non-VEGF growth factors, which may explain the differing enhancement pattern of some invasive lobular carcinomas compared with other breast cancers (63). Other well-differentiated invasive carcinomas may not induce a significant angiogenic response owing to their slow growth rate, which may account for their nonvisualization at MRI. Indeed, out of the five invasive carcinomas not visualized at MRI in the study by Wurdinger et al (23), four cancers were invasive lobular and one cancer was an invasive tubular carcinoma.

Similar differences in neovascularization and VEGF expression have also been observed in DCIS, which may account for the nonvisualization of some DCISs at MRI. High-grade DCIS has been more often associated with strong VEGF expression than has low-grade DCIS (28,64), which may explain why some cases of DCIS, particularly low-grade DCIS, are occult at MRI. Several studies have reported nonenhancement associated with known breast cancers on MR images (5,23,39,40,63). Additionally, MRI-occult breast cancers have been reported in some studies of patients undergoing bilateral prophylactic mastectomies, resulting in unexpected cancer diagnoses. For example, in a study by Yamauchi et al (65) of patients undergoing bilateral prophylactic mastectomy owing to history of hereditary breast and ovarian cancer, the authors reported that unsuspected breast cancers were found in 11.3% (six of 53) prophylactic mastectomy specimens following surgery, despite the patients undergoing presurgical mammogra-

phy, US, and MRI with negative findings. Of the six unsuspected cancers, five lesions were DCIS and one lesion was a 0.5-cm invasive carcinoma, confirmed at histologic analysis (65). Given that not all cancers may be visualized at MRI, it is important to recognize the limitations of the modality.

It is critical to emphasize to high-risk screening patients, who may undergo alternating screening mammography and MRI, that mammography and MRI are complementary examinations and that mammography should not be skipped in favor of only MRI. Similarly, MRI should not be performed as a shortcut for resolving a true mammographically or sonographically suspicious finding in lieu of biopsy, as false negatives may occur. If there is a truly suspicious imaging finding or a change at imaging, biopsy should be recommended by using the modality in which the finding was best visualized.

Conclusion

Although MRI remains the most sensitive modality for the diagnosis of breast cancer, false-negative results may occur. These occur primarily owing to perceptual errors, cognitive errors, or nonvisualization of the lesion secondary to nonenhancement. Developing and adhering to a thorough search pattern, which should also include extramammary regions, is critical to avoid missed cancers. To avoid cognitive errors, readers should ensure they obtain a thorough clinical history, review all imaging sequences in all planes (including MIP images), and use all available comparison examinations to detect subtle changes over time. Despite this, a small number of false-negative cases are inevitable, as certain cancers may not demonstrate significant contrast enhancement. While breast MRI represents a valuable diagnostic tool, it is important that radiologists recognize the potential limitations of the modality to avoid missed cancers.

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