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Contrast-enhanced breast MRI: factors affecting sensitivity and specificity

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Abstract. Contrast-enhanced MRI (CE-MRI) of the breast has been investigated for over 10 years. The reports of sensitivity for cancer detection have generally been greater than 90 %. However, estimates of specificity have varied greatly. Differing results are due to differences in study populations, technical methods and criteria for interpretation. Early and marked signal rise, detected using dynamic imaging technique following contrast administration, is the MRI hallmark of cancer. However, some malignant lesions may enhance slowly or minimally, and a variety of benign lesions may enhance rapidly with marked signal intensity. High resolution techniques generally requiring longer acquisition times are more likely to depict the slowly enhancing malignancies at the cost of a decrease in specificity due to lack of temporal resolution. This disadvantage may be offset by the improved visualization of lesion morphology with high resolution images. This report reviews the methods and results of the leading investigators of breast MRI.

Key words: Breast neoplasms, diagnosis – Breast neoplasms, MR – Magnetic resonance (MR) contrast enhancement

Introduction

Since contrast-enhanced MRI (CE-MRI) of the breast was first described in the mid-1980's, numerous investigators have reported their experience with this modality, showing that MRI can depict even the smallest of breast cancers. However, estimates of accuracy have varied with a wide range of statistical values reported. The sensitivity of contrast-enhanced MRI for detection of breast carcinoma has been uniformly high with reports generally above 84 %, most above 93 % [1–13]. Specificity values have fallen into a wider range, 37–97 % [1–12]. These differing results are in part due to large differences in MR imaging protocols, as well as differences in diagnostic criteria. The variables in technique include system field strength, unilateral versus bilateral scanning, type of breast coil, imaging parameters, dose of contrast agent, bolus administration versus slow infusion of contrast agent, timing of contrast administration with imaging, acquisition times, slice thickness, use of fat suppression, subtraction or other post-processing techniques, and composition of study populations. Although there is universal agreement that the majority of cancers will be identified with MRI, there is a lack of consensus regarding the appropriate indications and optimal imaging protocol for this modality.

Basis for use of contrast in breast MRI

Successful breast tissue differentiation with MRI has been based on the use of gadolinium-chelate intravenous contrast agents which are distributed throughout the extracellular space, accumulating in areas of high blood flow and marked capillary permeability and leakage space. Malignant tumors less than three millimeters in diameter will stimulate the growth of new blood vessels by secreting angiogenesis factor [14]. These tumor vessels often develop anastomoses and shunts resulting in low vascular resistance which results in increased diastolic flow and, in some cases, high systolic flow which can be identified with Doppler ultrasound technique [15–19]. The angiographic appearance of malignant neoplasms of various tissue origins includes neovascularity, venous laking, early venous drainage (arteriovenous shunting), and perivascular cuffing, whereas the absence of neovascularity suggests benignity [20]. Angiographic investigation specifically of the breast has led to similar conclusions [21–23].

Comparison of CE-MRI of various breast lesions with histopathology has revealed a correlation of amplitude and rate of enhancement with microvessel density. Buadu et al. correlated enhancement with tumor vascularity in 63 lesions, showing that malignancies tended to

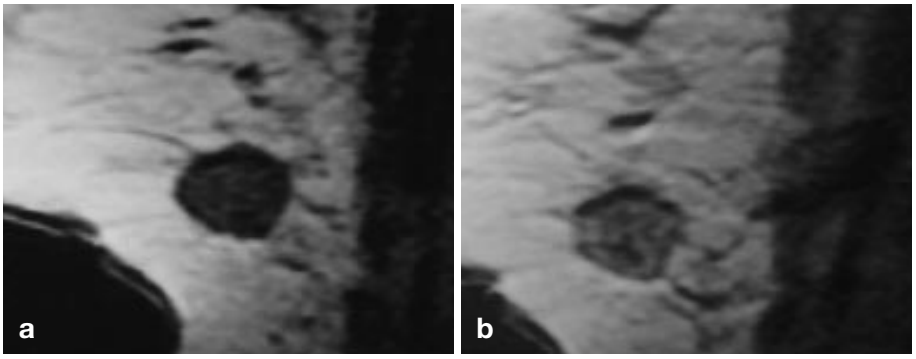

Fig. 1 a, b. Atypical delayed enhancement of maligancy. Sagittal, pre-contrast **(a)**, and 3 min 15 s post-contrast **(b)** T1-weighted 3D fast spoiled gradient echo (22/5.0; flip angle 40°). High grade invasive ductal carcinoma is seen as a slowly enhancing, irregularly marginated mass with spiculation. No enhancement occurred in the first 95 s of scanning. There is minimal enhancement in b, the second post-contrast image. (From [30] with permission)

enhance far more rapidly and contained far greater microvessel densities than benign lesions [24]. However, 3 of 51 malignant masses enhanced slowly (infiltrating lobular carcinoma, mucinous carcinoma, and invasive ductal carcinoma with extensive periductal elastosis), and microvessel count was significantly lower in these tumors than in the rapidly enhancing malignancies (Fig. 1).

Common benign conditions

False positive examinations whether by physical examination, mammography, sonography, or MRI can cause great distress to the patient and great expense to diagnose. Unfortunately, many of the benign conditions which may cause concern by clinical or traditional imaging evaluation, may be problematic with CE-MRI. The more common benign conditions with potential for false positive interpretation are reviewed.

Hormonal influence on breast tissue

The variation in breast tissue composition with menstrual cycle has been studied with unenhanced MRI [25–27]. The breast undergoes marked changes during the course of a menstrual cycle. Several days following menses, the breast contains dense cellular stroma, and closed ductal lumens, while during the second half of the cycle, the stroma becomes loose and edematous and ducts dilate with secretory material. There is an increase in sprouting and budding of ducts during days 15 to 20, probably related to progesterone stimulation [28]. Significant but variable changes occur in T1, but not T2, of glandular tissue with progression of the menstrual cycle [26, 27]. Parenchymal T1 relaxation time and water content have been shown to be at a minimum between days 6 and 15, peaking after day 25 [25].

In one study, 80 % percent of healthy asymptomatic premenopausal women studied with CE-MRI at various times of their menstrual cycles had one or more enhancing foci, three-quarters of which resolved during follow-up studies, and 45 % enhanced at a rate beyond an established threshold for malignancy [29]. Since the parenchymal tissue is relatively quiescent immediately following menses, we suggest patients set their MRI appointments for a week following onset of menses, but in actual practice, this limitation is impractical. Although the early enhancement of neoplasia can usually be identified with dynamic imaging, the gradual patchy enhancement which occurs in premenopausal women is potentially confounding. Significant disease may be obscured by surrounding enhancing tissue if imaging is delayed even for a min or two after contrast administration [30]. The normal parenchymal breast tissue of postmenopausal patients enhances minimally, leaving a bland background for detection of enhancing lesions. Hormonal replacement therapy may reduce this advantage. Several studies have examined the mammograms of women treated with estrogens or a combination of estrogens and progesterone showing a marked increase in fibroglandular tissue in 17–25 % of these patients [31–33]. This parenchymal activity could affect contrast uptake and MRI interpretation, although this has not yet been well studied.

Benign breast masses

Fibroadenomas are composed of fibrous stroma, proliferating ducts and acinar tissue [34]. Fibroadenomas evolve from proliferation of multiple lobules. The epithelial and stromal components are present in varying amounts with either adenomatous, fibrous or myxoid predominance. The septations noted within enhancing fibroadenomas on MRI may be related to the margins of the adjacent proliferating lobules [35]. Enhancement patterns among the various histological subtypes using contrast-enhanced MRI has been noted as follows [36]: (1) Myxoid tumors tend to show rapid and strong enhancement, similar to carcinoma. (2) Fibroadenomas with a predominance of glandular components are intermediate in speed and amplitude of enhancement, while the predominantly fibrous type enhance very little. (3) Fibroadenomas in premenopausal patients tend to exhibit significant enhancement presumably because of continued biological activity of the tumor, while those in older women tend to exhibit minimal enhancement. Because of this variability, specificity for the diagnosis of fibroadenoma is not greatly improved with MRI. Malignancy may be excluded only when insignificant enhancement occurs.

Solitary papillomas, almost always benign, are formations of epithelial fronds supported by a fibrovascu-

lar stroma, generally located in the subareolar region of major ducts [37]. Multiple papillomas or papillomatosis involve multiple terminal duct-lobular units and are associated with increased risk of breast cancer. The morphologic characteristics, amplitude and speed of contrast enhancment on MR imaging have been found to be similar for benign or malignant papillomas, other malignancies and fibroadenomas [36]. The use of MRI in the evaluation of papillomatosis for determining disease extent, rather than malignant potential, has been described [38].

Changes in the breast resulting from open-biopsy, radiation or chemotherapy include variable degrees of stromal fibrosis, hyalinization, vascular alterations, and fat necrosis [39]. Enhancement of affected tissue will occur for 6 months or more following excisional biopsy and for as long as 18 months following radiation [31]. Fat necrosis may clinically simulate carcinoma by manifesting as a palpable mass which may be detectable mammographically as a new mass, architectural distortion, calcium deposition or "oil cyst" [40]. Microscopically, damaged fat cells are surrounded by histiocytes and giant cells with or without acute inflammatory cells [34]. In the acute stages of fat necrosis, significant contrast enhancment may be seen on MRI [36].

Other benign tumors of the breast are less common, but may be difficult to characterize by any imaging modality. Cystosarcoma phylloides (phylloides tumor) is composed of benign epithelial elements and a spindle-cell stroma which is more cellular than fibroadenomas [34]. About 16 % of histologically low grade tumors recur following excision, and approximately 7 % of high grade lesions metastasize. There is great difficulty in the accurate prediction of the biological behavior and prognosis of phylloides tumors based on the variable histopathological appearance of individual tumors. On CE-MRI phylloides tumors tend to display rapid contrast enhancement and inhomogeneous but high signal intensity [36, 41]. It is unlikely that the potential for recurrence or metastasis may be predicted using MRI with a greater degree of accuracy than histopathological evaluation. Breast hamartomas are usually diagnosed by mammography as encapsulated inhomogeneous masses containing fat. If detectable fat is absent, both the mammographic and MRI diagnosis is difficult [42]. Contrast enhancement of hamartomas is variable and inhomogeneous depending on the amount of adenomatous change [36].

Benign proliferative breast disease

The term proliferative "dysplasia" represents such benign histopathological findings as sclerosing adenosis, apocrine metaplasia, epithelial hyperplasia, and lobular neoplasia. These benign, occasionally enhancing breast lesions may show significant contrast enhancement and may be a source of false positive MRI findings [36, 43]. The range of disease includes moderate intraductal or extraductal proliferation, associated with a slight increased risk of malignancy to high-grade proliferation, considered precancerous or a high-risk marker [44]. The MRI appearance of these proliferative changes seems to parallel the pathological distribution when enhancement occurs [36].

Scientific investigations

For whole breast CE-MRI, the bulk of breast MRI investigations have utilized one of two basic technical approaches: static three-dimensional (3D) high resolution imaging or dynamic two-dimensional (2D) imaging. With dynamic technique initial imaging is generally completed within a few seconds to 1 min after rapid bolus administration of contrast with subsequent repetitive imaging for several minutes [1, 4–11, 45]. This approach allows analysis of rise in signal intensity over time within a given lesion. Higher resolution may be obtained with 3D imaging, which has the theoretical advantage of improved morphological evaluation and of small lesion detection since this technique allows for thin slice thickness, minimizing volume averaging. However, these advantages are offset by a prolonged acquisition time [3, 46]. Gadopentetate dimeglumine (Gd-DTPA) has been used in the majority of investigations in dosages ranging from 0.1 to 0.2 mmol/kg body weight, but other gadolinium-chelates have been studied as contrast agents for breast imaging. Virtually all investigators have utilized either commercially available or modified surface coils for breast imaging.

Static, high resolution imaging

Reports of the ability to differentiate carcinoma from benign tissue with CE-MRI came first from Germany by Heywang et al. [47, 48] in 1986, who used a spin echo T1-weighted sequence before and after the administration of intravenous Gd-DTPA, with an imaging time of approximately five minutes and a slice thickness of 5 mm. With the development of fast T1-weighted gradient echo pulse sequences, "dynamic" MR whole breast imaging became feasible. In 1988, this group [49] reported that all carcinomas in a group of 60 patients exhibited early intense signal enhancement using this technique. Significant contrast uptake associated with variable rates of enhancement were found with fibroadenomas. Gradual enhancement was generally seen with proliferative and non-proliferative dysplasias. However, later reports from the principal investigator indicate that a less than 100 % sensitivity using dynamic technique prompted abandonment of this approach [50].

With advances in MR technology, Heywang-Köbrunner has favored a static 3D FLASH (fast low angle shot) technique which offers an imaging time of under 3 minutes and high resolution with thin slice thickness [50, 51]. This approach may detect the occasional carcinoma which does not enhance in the typical rapid, intense pattern. A review of 400 biopsy-proved lesions showed that all carcinomas enhanced strongly, all but 5 % rapidly, and 85 % focally [52]. Over 70 % of benign tissues did

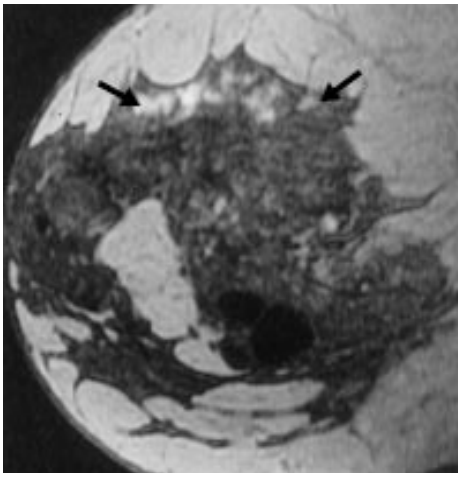

Fig. 2. Invasive carcinoma with extensive intraductal component. Sagittal, 3D inversion recovery prepared gradient echo (19.1/5.9; TI 150), 2 min 17 s acquistion, first post-contrast image. A broad band of irregularly marginated enhancing tissue *(arrows)* is present. Note the similarity of appearance to scar tissue in Fig. 3. (From [30] with permission)

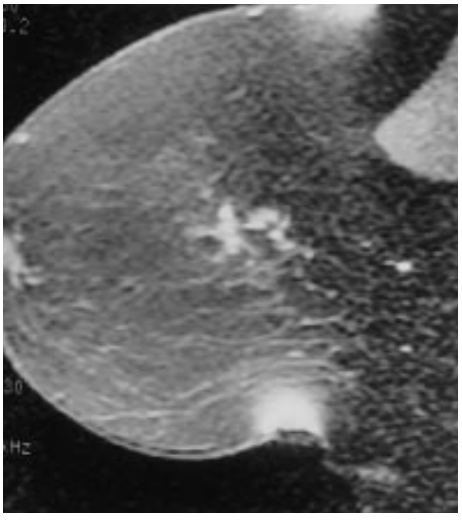

Fig. 3. Enhancement of scar tissue. Sagittal, fat suppressed T1-weighted 3D fast spoiled gradient echo (24.2/4.2; flip angle 30°), 3 min 19 s acquisition, first post-contrast image. Irregularly marginated enhancing tissue is present in this patient who underwent surgical biopsy six months previously and recently finished a course of neoadjuvant chemotherapy for invasive carcinoma. Pathologic evaluation of the subsequent mastectomy specimen revealed only scar tissue. (From [30] with permission)

not demonstrate significant contrast uptake, although some benign tumors and proliferative dysplasias enhanced strongly. In another report of 565 mammographic or clinical problem cases, MR was helpful in guiding the evaluation of 403 patients who demonstrated either marked focal enhancement suggestive of significant disease, or little enhancement consistent with benign tissue [53]. For these cases, the sensitivity for cancer improved from 56 % with mammography to 100 % with MRI, and the specificity increased from 48 % to 74 %, respectively. Based on this experience, Heywang-Köbrunner has offered several points of advice [36, 50]: (1) regardless of the enhancement rate, the presence of high amplitude, focal enhancement is suggestive but not diagnostic of malignancy and should prompt further work-up; (2) management of breasts with strong diffuse enhancement should be determined by mammography, clinical findings and symptoms; (3) MRI should be reserved as a method for resolving ambiguous findings at traditional breast work-up; (4) findings such as mammographically detected microcalcifications, well-circumscribed tumors and inflammatory lesions are inappropriate for MR evaluation.

Enthusiasm for breast MRI in the United States increased in 1991, when Harms and colleagues introduced new methods for dramatic high resolution 3D images of the contrast enhanced breast first using a combination of fat suppression and magnetization transfer [46, 54], and later using the refined RODEO technique (rotating delivery of excitation off resonance), a robust method for fat suppression with T1 weighting, ideal for use with gadolinium contrast studies [3]. Using RODEO, initial investigation resulted in a sensitivity for cancer foci detection of 94 % and a specificity of 37 % [3]. False positive findings in this study included fibroadenomas, benign lymph nodes, proliferative and non-proliferative fibrocystic change, sclerosing adenosis, atypical hyperplasia and lobular carcinoma in situ (lobular neoplasia). Additional cancer foci were identified relative to mammography. However, specificity with this technique was low, which may be explained by the experimental methods and inclusion criteria for positive studies. The RODEO method at that time required a long acquisition time of approximately 5 min allowing contrast accumulation in any relatively hypervascular tissue, and perhaps most importantly, findings were considered positive simply if signal intensity was greater than surrounding breast parenchyma on the post-contrast images [3]. The difficulty of lesion differentiation with prolonged acquisition times is illustrated in the comparison of Figs. 2 and 3.

Orel et al. [35] examined the MR findings of 19 carcinomas and 14 fibroadenomas scanned dynamically with 2D technique and with high resolution 3D technique. This group found no statistically significant difference between time/intensity curves of benign and malignant lesions. Because of this overlap, Orel's group eliminated dynamic acquisition in favor of high resolution 3D imaging using a 256×512 matrix and 3 to 5 min imaging times [55]. Certain architectural patterns which could prove to be diagnostic were noted; rim enhancement within some carcinomas, and internal septations within fibroadenomas [35].

Dynamic imaging

Despite the successful experience of several prominent researchers using 3D high resolution imaging, the use of dynamic technique is favored by many. Dynamic technique has been advocated by Kaiser of Germany who, in 1989, reported preliminary sensitivity and speci-

ficity values above 95 % (1). A year later, Stack et al. reported their experience with 18 patients using single slice T1 weighted spin echo imaging (acquisition time 12.4 s), before and continuously after rapid bolus contrast administration [45]. The time/signal intensity curves revealed rapid intense enhancement of the malignancies, gradual intense enhancement of the single fibroadenoma studied, and gradual mild contrast uptake in benign dysplasia. These results corroborated the findings of Kaiser, suggesting that dynamic imaging could accurately differentiate benign from malignant breast disease. In 1992, Kaiser and Reiser reported on almost 1000 examinations performed dynamically with sensitivity 98.3 %, specificity 97.0 %, positive predictive value (PPV) 82.1 %, and accuracy 97.2 % [56]. False positive findings included fibroadenomas, proliferative dysplasia, acute mastitis, fresh scar and pathologically "normal" tissue [56, 57]. However, the reported 82 % PPV appeared to represent a marked improvement over the PPV for mammographically identified lesions, which is no greater than about 30 % in the United States [58]. These findings created a flurry of investigative activity aimed at decreasing the biopsy rate for lesions found suspicious at mammography.

Numerous investigators have attempted to quantify the rate and rise of signal intensity in dynamic contrast studies by various methods. Turkat et al.,using an experimental design similar to Kaiser's protocol with 54 s acquisitions, reported that the most accurate benign/malignant differentiation occurred between 1 and 2 min with a 100 % sensitivity and 83.3 % specificity, a positive result defined as 90 % enhancement in that time period [9]. Fischer et al. evaluated the signal/time ratios at dynamic 2D MR imaging by developing a point system to quantitatively evaluate enhancement within the first and second minutes after contrast administration, delayed enhancement, and the pattern of enhancement [4]. This scoring system resulted in two false negatives (both in situ carcinomas), and two false positives (fibroadenomas) with sensitivity of 95.3 % and specificity of 89.5 %. Kelcz et al. described a normalized kinetic order of the rise rate of signal intensity, and derived a threshold value that identified 3 of 3 carcinomas, and included one false positive of 24 benign lesions , but later reported one false negative using this parameter, and cautioned against the use of MRI as a substitute for mammography [5, 6]. Flickinger et al.,imaging at up to 45 s intervals following contrast administration, described a maximum intensity change per time interval ratio (MITR), and found that 3 of 8 fibroadenomas and 1 of 3 fibrocystic cases were within the same MITR range as all ten cancers with a calculated specificity of 66 % [7]. At our institution, the experience of dynamic contrast enhanced MRI for differentiation of benign from malignant mass lesions has been disappointing. Our protocol initially included a multiplanar spoiled gradient echo series with an acquisition time of 30 to 45 s. We found marked overlap of the time/intensity curves among cancers and benign lesions. Reactive lymph nodes displayed the greatest amplitude of signal intensity in the first min post-contrast injection [30, 59]. Stomper et al. showed the variability of sensitivity, specificity, accuracy and predictive values for different points on the time/intensity curve for 51 lesions, concluding that these curves showed no significant difference between benign and malignant lesions [11].

For diagnostic protocols dependent on user-defined range-of-interest measurements (ROI), placement of the ROI is critical for accurate diagnosis [60]. Since malignant tumors can show internal variation in enhancement amplitudes, the ROI must be placed in the areas of maximal enhancement and areas of submaximal enhancement or whole lesion assessment should be avoided. Avoiding ROI measurements, a few investigators have looked at timing of enhancement as diagnostic criteria. Gilles et al., using a 47 s acquisition time, considered a positive finding as enhancement occurring simultaneously with blood vessel enhancement, and reported a 95 % sensitivity and 53 % specificity [61]. One tubular carcinoma and two lobular carcinomas did not show enhancement, and 37 of 79 benign lesions showed enhancement concomitant with vascular uptake. Boetes et al. also used blood vessel enhancement as a reference, but also considered internal enhancement pattern of the lesion as diagnostic criteria [8]. This group, using a single section, 2.3 s acquisition, defined a positive finding as lesion enhancement at 11.5 s after enhancement of the aorta, with the result of missing a slowly enhancing 10 mm ductal carcinoma in situ, a non-enhancing 2 mm invasive ductal carcinoma and a non-enhancing 40 mm invasive lobular carcinoma. However, specificity was improved by observing a "benign" pattern of enhancement that started in the center and progressed peripherally in 4 of 10 fibroadenomas despite rapid contrast uptake.

Other experimental methods

A combination of rapid acquisition with techniques which preserve high spatial resolution may improve specificity by allowing evaluation of lesion morphology as well as enhancement patterns. A whole breast imaging technique which allows acquisition times of under 15 s by partial sampling of the central region of k-space superimposed on high resolution 3D images has been described [62]. However, artifacts may occur with reduced sampling of k-space which affect visualization of small lesions [63]. Echo-planar imaging used to study dynamic lesion enhancement characteristics combined with conventional high resolution imaging has also been described [10].

Methods to evaluate other parameters of vascularity are also under study. Early reports by different groups investigating vascular permeability in breast tumors suggest that the consideration of functional tissue parameters may allow more refined benign/malignant differentiation [10, 64, 65]. As with other roads of investigation, the most appropriate technique for functional analysis is not yet established. Notably, Hoffmann et al., in contrast to the majority of investigators using dynamic technique, advises a slow, constant-rate infusion, rather than a rapid bolus injection, arguing that

the faster injection rate is of the same order of magnitude as the wash-in time of some tissues, and only the slower infusion resulting in a prolonged lower contrast plasma level would allow analysis of response as a function of time [64]. Hulka et al., have published results on the greatest number of lesions to have undergone analysis of permeability using echo-planar technique. This group reported an 86 % sensitivity and a 93 % specificity using a pre-determined value for the extraction-flow product, a quantification of a model describing the physiologic mechanism of contrast uptake [10].

Other factors may affect the final images available for diagnostic review. The use and type of breast coil varies among investigators. If phased-array capability is unavailable, signal-to-noise ratios will be optimized with unilateral scanning, rather than bilateral. Although many investigators have imaged the entire breast or both breasts, others have reported their dynamic data based on imaging only through the lesion in question.

The appropriate dosage of contrast has been addressed by few investigators, with only one published study suggesting an optimum dose of 0.16 mmol/kg of Gd-DTPA for 3-D FLASH imaging [66]. Optimum dosages for other sequences and other contrast agents remain unknown. Fat suppression improves lesion conspicuity but can be problematic due to field inhomogeneities, but various forms of fat suppression are used by different researchers [3, 10, 55, 67]. Subtraction for elimination of fat signal increases conspicuity, but this post-processing technique is not yet readily available from all MRI manufacturers [68]. Finally, patient motion between pre- and post-contrast acquisitions may result in interpretative errors. An algorithm to correct for motion has been described [69].

Conclusion

CE-MRI of the breast has been investigated for over 10 years by many radiologists using different study populations, different technical methods and different criteria for interpretation. Although the variable biological behavior of both benign and malignant lesions can be confounding, sensitivity for cancer is acknowledged to be high with CE-MRI and specificity is thought to be greater than with mammography. Yet, a consensus has not yet been reached regarding the indications, the performance, or the diagnostic criteria for this examination. Therefore, it is an examination which remains an investigative technique, attempted with caution but largely avoided by the typical MRI or breast imaging radiologist. The MR examination is expensive and uncomfortable for the patient. Interpretation can be difficult for the radiologist, and since a method for sampling suspicious enhancing tissue is not available to most imaging centers, a positive examination may cause great distress for the patient and great frustration and worry for the referring physician as histological proof of significant disease may be unattainable. Furthermore, although our imaging methods and diagnostic accuracy may be improving, experience with the conventional breast imaging modalities suggests that despite imaging diagnoses of high specificity, patients and their physicians desire pathological proof of disease [70]. Only when standards for imaging and interpretation are developed and MR-guided biopsy techniques are available can the process of large-scale, multi-institutional clinical trials be launched to determine efficacy of the technique. Given the current protocols, the cost, in money and in time spent scanning the patient and interpreting the examination, makes MRI an impractical tool for breast cancer screening. Therefore, in coming few years, CE-MRI is likely to remain the imaging approach used only after mammography and sonography are proved non-diagnostic for the work-up of specific problems in individual patients.

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