Chapter 9
In Situ Disease on Breast MRI

Heather I. Greenwood and Bonnie N. Joe

Abstract Ductal Carcinoma in Situ is a non-invasive form of breast cancer, in which malignant ductal epithelial cells proliferate, but do not invade through the basement membrane. It is a heterogeneous disease, and is a non-obligate precursor to invasive carcinoma. With the advent of screening mammography the incidence of DCIS has greatly increased. MRI is the most sensitive examination for detecting DCIS. The most common presenting morphology of DCIS is nonmass enhancement, with a clumped internal enhancement pattern and with a segmental distribution pattern. There is great variety in the kinetic patterns of DCIS, and therefore assessment must be based on morphology. Additional tools, such as diffusion weighted imaging have been shown to be promising in helping detect clinically relevant DCIS.

Keywords Ductal Carcinoma in Situ (DCIS) • MRI • Nonmass enhancement • Clumped internal enhancement • Clustered ring internal enhancement • Segmental distribution • Diffusion Weighted Imaging (DWI) • Overdiagnosis • Overtreatment • Oncotype DX 12-gene assay (DCIS Score)

9.1 Background

Ductal carcinoma in situ (DCIS) is a noninvasive breast cancer, referred to as stage 0 breast cancer. At pathology DCIS shows the proliferation of malignant ductal epithelial cells that line a terminal ductal lobular unit without evidence of invasion

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through the basement membrane. DCIS represents a broad spectrum of disease, and is a non-obligate precursor to invasive breast cancer [1–3]. Some lesions may remain clinically quiescent, while others are precursors to invasive breast cancer.

DCIS is rarely symptomatic. With the advent of screening mammography, there has been a significant increase in the incidence of DCIS from 18.7 per 100,000 in 1973–1975 to 32.5 per 100,000 in 2005 [4], a 17-fold increase. DCIS now accounts for up to 25 % of screen detected breast cancers [5].

The term DCIS includes a markedly heterogeneous group of lesions which differ in genetic and molecular abnormalities, histopathologic features, and biologic markers [6]. DCIS is classified according to its tumor grade (high, intermediate, low) architectural pattern (solid, cribiform, papillary, micropapillary, comedo-type), and the presence or absence of necrosis.

Despite the fact that not all cases of DCIS progress to IDC, women who have been diagnosed with DCIS report similar psychologic morbidity as women with invasive cancer [7, 8]. With this similar psychologic morbidity as well as the great heterogeneity of DCIS, there is currently a significant controversy regarding the clinical significance of DCIS, as well as the possible overdiagnosis and overtreatment of DCIS.

The definition of overdiagnosis is “the detection of cancers that would never have been found were if not for the screening test” [9]. Overdiagnosis is considered a harm of screening mammography, and may be considered the most adverse outcome of screening mammography. Autopsy series of women not known to have breast cancer in their lifetime show a prevalence of DCIS of about 10–15 % [10–12].

It is not possible to recognize which cases of breast cancer are cases of overdiagnosis at the individual level; the number may only be estimated at a population level based on data from years of screening mammography. Puliti et al. conducted a literature review of observational studies providing estimates of breast cancer overdiagnosis in a European population based mammographic screening program. The analysis of the papers in the review and of the biases that may affect the estimates found that the most likely estimate of overdiagnosis, “expressed as a percentage of the expected incidence in the absence of screening”, was low, and ranged from 1 to 10 %. The authors found the much higher estimates of overdiagnosis in the literature they reviewed to be related to “the lack of adjustment for breast cancer risk and/or lead time bias” [13].

An additional factor in over diagnosis may be secondary to high inter-observer pathologist variability and discrepancies in the classification of DCIS [14–20]. Several of the discrepancies in this classification come from the criteria used to distinguish between atypical ductal hyperplasia (ADH) and DCIS [17]. The architectural appearance and extent of disease process are not simultaneously present in ADH: the diagnosis of ADH is therefore made when some features of DCIS are present, however others are absent [21, 22]. Rosai et al. reported an “unacceptably high” interobserver variation between experienced pathologists in the context of ADH versus DCIS categorization [19]. Thus the issue of over diagnosis, is one shared by both radiologists and pathologists.

Despite the heterogeneous nature of DCIS, it has been shown that almost all invasive cancers arise from DCIS [23]. Long term (30 year) follow-up of low grade DCIS treated only with biopsy without definitive excision or radiation therapy demonstrates a 30–60 % incidence of IDC, usually at or near the site of DCIS [24]. Half of recurrent cases of DCIS lesions manifest as invasive cancer, and 20 % of DCIS cases result in distant metastatic disease in 10 years [25]. It is therefore essential to have an accurate test for the diagnosis and detection of DCIS.

The goal of treating DCIS is to prevent the development of invasive cancer and to decrease the rate of local recurrence. Traditionally DCIS has been treated in most women with breast conservation therapy (lumpectomy) either with or without radiation therapy. Several randomized controlled trials have shown that adding radiation treatment following lumpectomy decreases the risk of local recurrence and invasive local recurrence by 50 % [26–31]. However, some patients at low risk of recurrence may not require radiation therapy.

A challenge in the treatment of DCIS is that clinical factors and pathologic features of DCIS have not been shown to consistently help clinicians determine patients at low risk. The Oncotype DX 12-gene assay (DCIS Score) is a multigene expression assay that generates individualized estimates of the 10-year risk of any local recurrence (LR). The score is generated from an algorithm that includes 12/21 genes in the Oncotype DX invasive assay. The Oncotype DX Score has been shown to predict local recurrence in patients who have undergone breast conservation therapy alone [32]. Therefore, the Oncotype DX score in combination with other well-established risk factors has the potential to be a useful tool in decreasing the overtreatment of DCIS.

9.2 Sensitivity of Imaging Modalities

An accurate assessment of the extent of DCIS is required for successful breast conservation therapy, as patients with positive margins after surgery and patients with residual synchronous foci of DCIS have an increased risk of recurrence. Several studies have shown that MRI is the most sensitive imaging examination for the detection of DCIS. The overall sensitivity of MRI for DCIS has been shown to be approximately 92 %, versus 56 % for mammography [33]. MRI detection is related to contrast uptake. Contrast uptake, or enhancement, is secondary to tumor vascularity, vessel density and permeability. Therefore, MRI, unlike mammography may detect not just calcified DCIS, but also noncalcified DCIS.

Over the past several years, studies have demonstrated the increasing sensitivity of MRI for detecting DCIS. Early studies looking at the sensitivity of MRI for DCIS were performed at a higher temporal resolution and lower spatial resolution, focused on mass lesions, and were also performed in patients with a new diagnosis of breast cancer, generally diagnosed by either mammogram or ultrasound [34]. More recent studies have used higher spatial resolution MRI technique, focused on nonmass enhancement distinct from background parenchymal enhancement (BPE),

and evaluated a high risk screening population. These more recent studies have shown a greatly increased sensitivity of MRI for detecting DCIS [33, 34].

Not only is MRI the most sensitive examination for the detection of DCIS but it's sensitivity increases with increasing histologic grade. MRI has been shown to have a sensitivity of 80 % for low grade DCIS, 91 % for intermediate grade, and 98 % for high grade DCIS [33]. Thus MRI is the most sensitive at detecting the type of DCIS that is most likely to progress to invasive carcinoma and to recur.

In addition, contrast enhancement is a biomarker of protease and angiogenic activity. There is increasing vascularity with increasing grades of DCIS. Protease activity is required to penetrate into the basement membrane and beyond it [35]. These factors suggest that DCIS detected on MRI may be more clinically relevant. Therefore, MRI may prove a useful tool in the evaluation of DCIS and may help to allay criticism of mammographic overdetection.

9.3 MRI Features of DCIS

9.3.1 Morphology

Given that MRI has been shown to be the most sensitive imaging modality for the detection of DCIS, it is important to recognize the various MR imaging presentations of DCIS. The most common presenting morphology of DCIS is nonmass enhancement, seen in 60–81 % of cases [36–38]. Nonmass enhancement (NME) is defined as enhancement of an area that is not a mass. The term NME has replaced nonmass like enhancement in the BI-RADS lexicon [39]. Nonmass enhancement is further defined by its internal enhancement pattern as well as its distribution. The most common internal enhancement pattern seen when DCIS presents as NME is a clumped pattern, defined as cobblestone-like enhancement with occasional confluent areas. This internal enhancement pattern is seen in approximately 41–64 % of cases presenting as NME (Fig. 9.1). Less frequently when DCIS presents as NME, it may present with a heterogeneous (16–29 % of cases) or homogenous (0–16 % of cases) internal enhancement pattern [36–38].

In the second edition of BI-RADS for MR, the internal enhancement pattern "clustered ring" has been added. This is defined as small rings of enhancement, which are clustered together (Figs. 9.2 and 9.3) [39]. A study by Tozaki et al. showed that this finding was seen in 63 % of cases of malignancy (including both invasive and non-invasive), versus only 4 % of benign cases. The specificity for malignancy of the finding of clustered ring enhancement was 96 % [40].

When DCIS presents as NME, the most common distribution pattern is a segmental distribution, seen in approximately 14–77 % of cases [36–38, 41]. This is defined as a triangular region of enhancement, apex pointing to the nipple, suggesting a duct or its branches (Fig. 9.4) [39]. It may also present less commonly in a

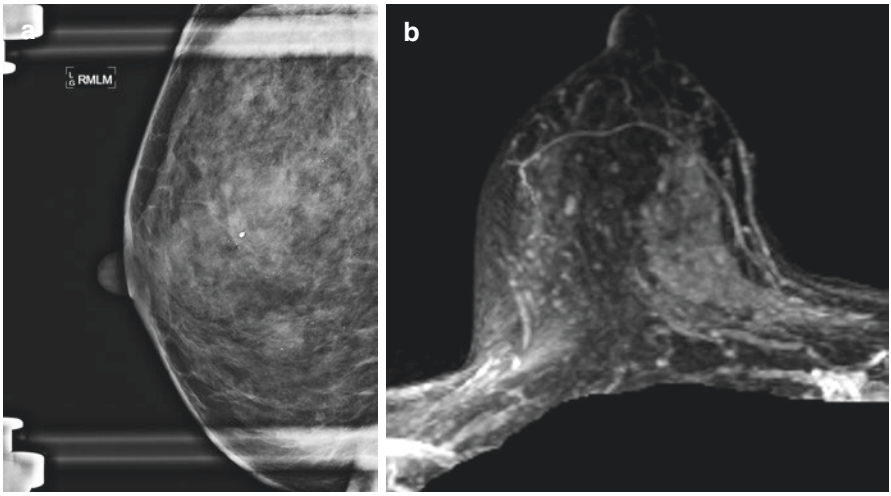

Fig. 9.1 High nuclear grade DCIS in a 47 year old found on screening mammography. (**a**) CC spot magnification view demonstrates segmental pleomorphic calcifications (**b**) MRI performed for extent of disease, maximum intensity projection (MIP) images demonstrates regional nonmass enhancement with a clumped internal enhancement pattern in the inner right breast

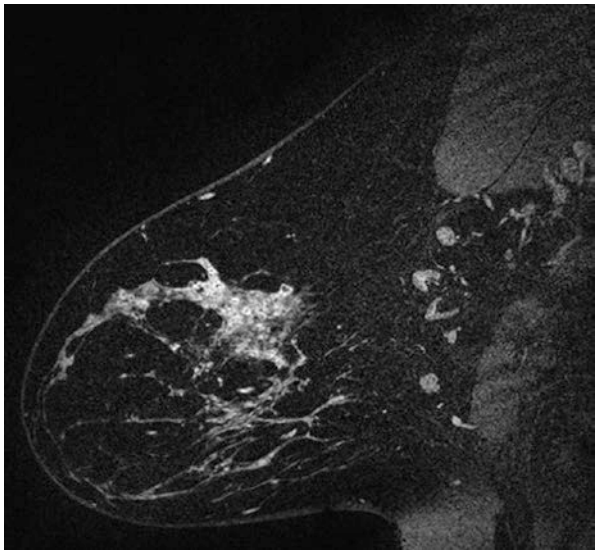

Fig. 9.2 Sagittal post-contrast subtracted image demonstrates segmental NME with a clustered ring internal enhancement pattern, compatible with biopsy proven DCIS in a 38 year old

linear, focal, regional, or diffuse enhancement pattern [36–38, 41]. The MR BI-RADS 2nd edition has removed the distribution ductal from the lexicon [39].

DCIS may also present as a mass morphology on MRI. A mass is defined as a 3D space occupying structure with convex outward contour, which may or may not displace or otherwise affect the surrounding normal breast tissue [39]. This morphology

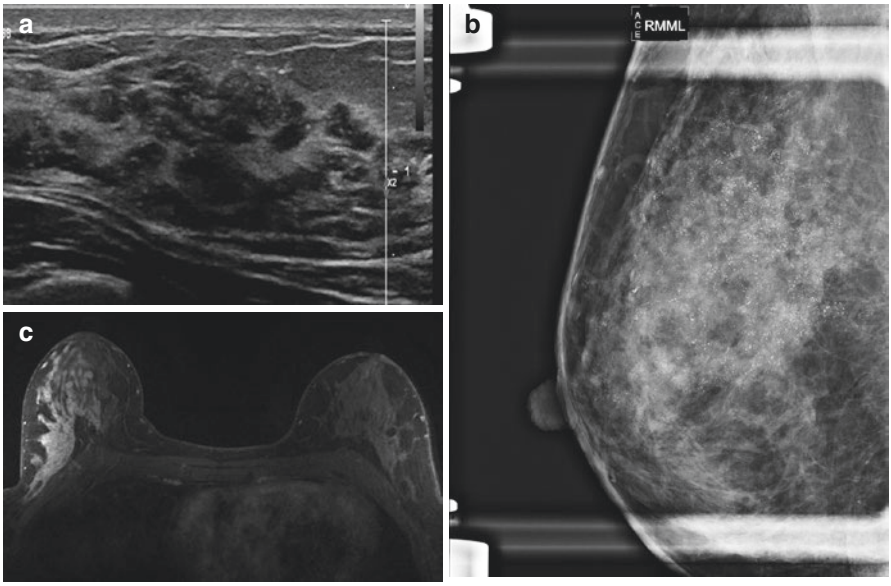

Fig. 9.3 28-year-old female with a palpable lump in the right breast. Given the patient's age she had an ultrasound examination to start. (**a**) Ultrasound images show an irregular mass containing multiple echogenic foci (**b**) Subsequently performed CC mammogram demonstrates fine pleomorphic calcifications. (**c**) MRI performed for extent of disease demonstrates regional NME with a clustered ring internal enhancement pattern, consistent with biopsy proven DCIS

has been seen in approximately 14–41 % of cases of DCIS on MRI [36–38]. Masses are further defined by shape, margin, and internal enhancement patterns. When DCIS presents as a mass on MRI it most commonly is an irregular mass, seen in 14–83 % of cases (Fig. 9.5). Less frequently it may present as an oval or round mass [36, 37, 42]. Of note, the 2nd edition of the MR BI-RADS lexicon has removed the shape lobular for mass lesions to be consistent with the mammogram and ultrasound sections. Masses with up to 3 lobulations now simply are described as "oval" [39]. The literature describes various mass margins when DCIS presents as a mass on MRI, including irregular (14–92 % of cases) and spiculated (0–92 % of cases) (Fig. 9.5). Infrequently DCIS presenting as a mass may have smooth margins (4–8 % cases) [36, 37, 42]. DCIS manifesting as a mass on MRI, may have various internal enhancement patterns. The most common pattern is heterogeneous (9–67 %), followed by homogenous (9–25 %), and less commonly rim enhancement (0–8 %) (Fig. 9.6) [36, 37]. To our knowledge, there has not been a report of non-enhancing dark internal septa in reports of DCIS seen as a mass on MRI. Of note, the terms central enhancement and enhancing septations have been removed from the new BI-RADS lexicon [39].

The least common morphologic appearance of DCIS is a focus [36–38]. A focus is defined as a lesion <5 mm, which is too small to further characterize (Fig. 9.7) [39]. The new BI-RADS edition has removed the term foci from the lexicon [39].

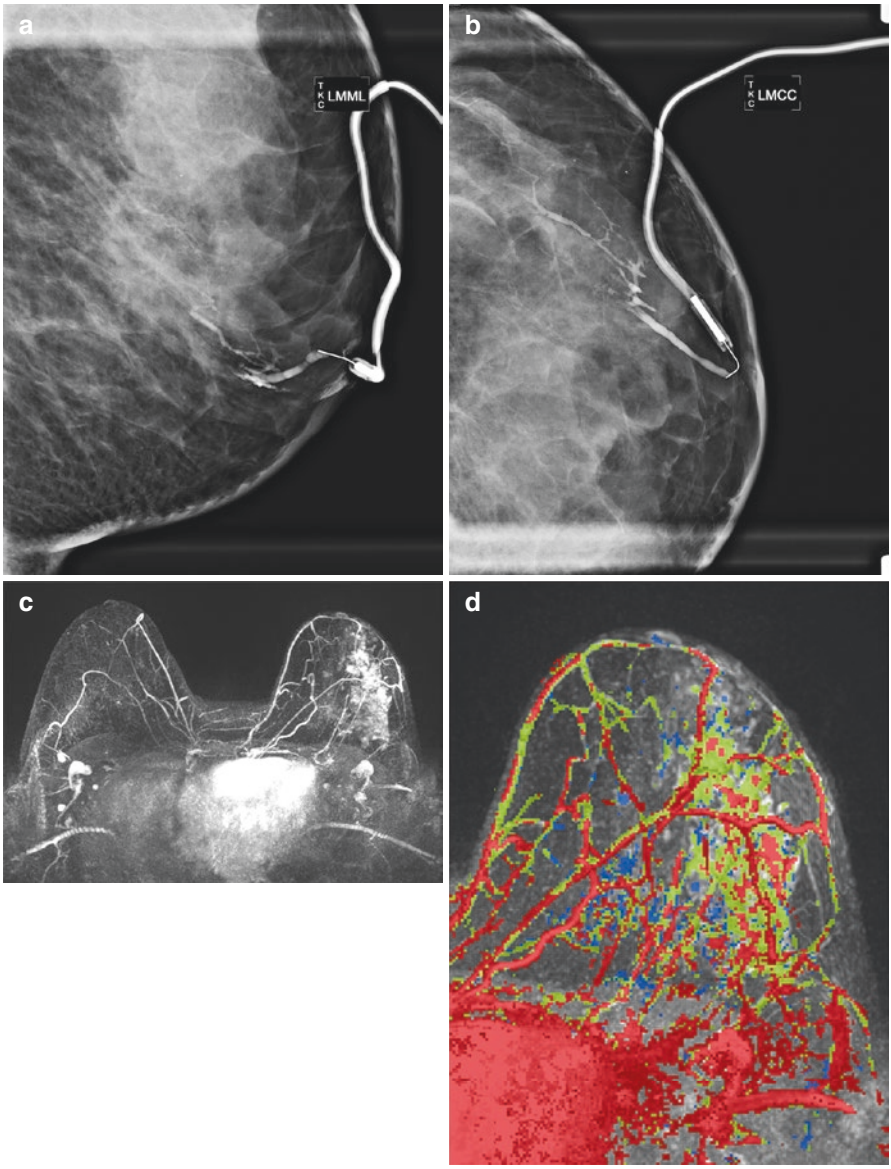

Fig. 9.4 34 year old with left bloody nipple discharge, normal mammogram and ultrasound. (**a**) LM and (**b**) CC views from a ductogram show an intraductal-filling defect in a slightly lower, slightly outer duct. Left duct surgical excision revealed IDC and DCIS on pathology. (**c**) MRI post-contrast subtracted MIP demonstrated extensive clumped NME with a segmental distribution (**d**) Kinetic image demonstrates mixed, predominantly Type 2 and Type 3 delayed kinetics. MR guided biopsy revealed DCIS and IDC. Kinetic key: Type 1 = *blue*, Type 2 = *green*, Type 3 = *red*

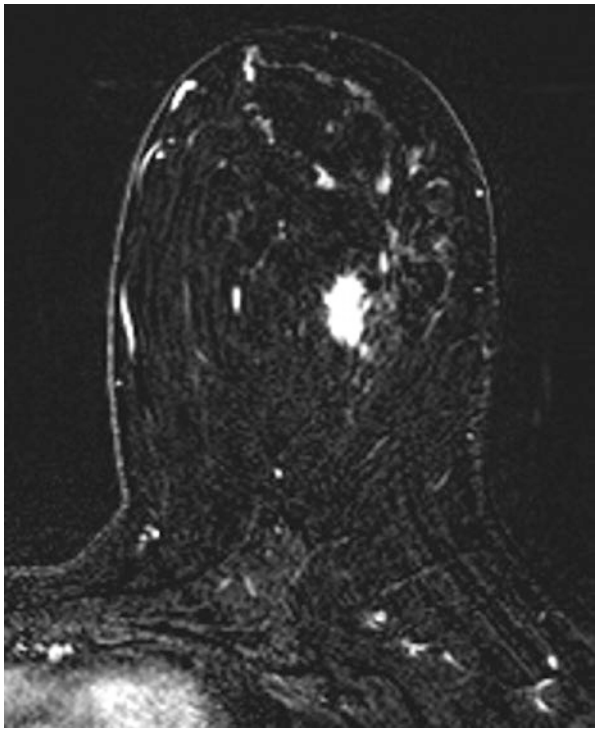

Fig. 9.5 Micropapillary DCIS in a 38-year-old woman with a palpable lump in the left breast. Post-contrast subtracted MR image shows an irregular mass, with spiculated margins, consistent with biopsy proven micropapillary DCIS

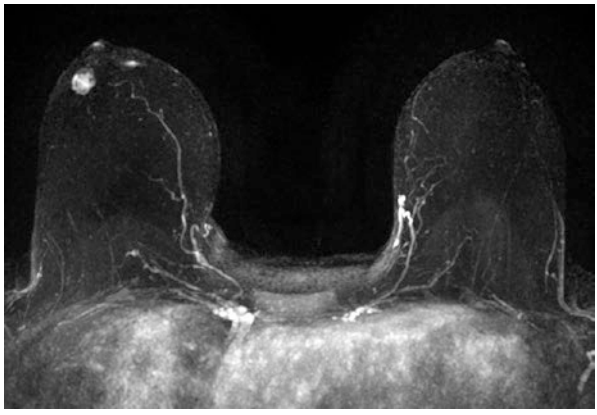

Fig. 9.6 High grade DCIS in a 38 year old female with new diagnosis of DCIS. Post-contrast MIP image demonstrates an oval mass with irregular margins and a heterogeneous internal enhancement pattern in the slightly outer right breast

Rosen et al. found that pure DCIS manifests as a focus in 12.5 % of cases while 3.0 % of invasive carcinomas manifest as a focus [38]. Van Goethem et al. found that a focus was seen in 20 % of DCIS cases versus 2.8 % invasive cancers [44]. Factors suggesting that a focus is malignant on MRI include: no T2 hyperintensity, lack of fatty hilum, washout kinetics, new or enlarging in size. Signs of benignity of

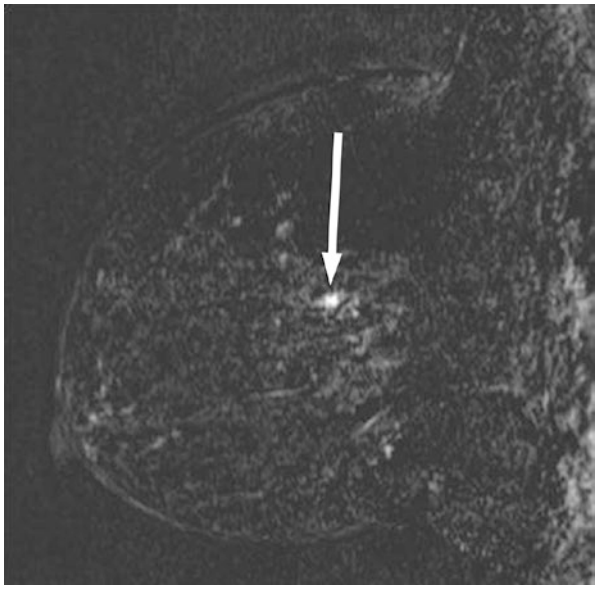

Fig. 9.7 Intermediate-grade DCIS in a 44 year old woman with negative mammographic findings who underwent screening MR imaging because of a strong family history of premenopausal breast cancer. Sagittal postcontrast subtraction image demonstrates a 4 mm focus that demonstrated type 3 (washout) kinetics (Reprinted with permission from Greenwood et al. [43], with permission from Radiology Society of North America (RSNA®))

a focus include: T2 hyperintensity, presence of a fatty hilum, persistent kinetics, and stability [39].

Jansen et al. found that there was no statistically significant difference between MR morphology in low, intermediate, and high nuclear grade DCIS lesions [36]. Additional studies by Chan et al., and Rahbar et al., also found no significant difference in MR morphology between high grade and non-high grade DCIS [37, 45]. At this point, no study to our knowledge has shown that MR morphology is able to predict nuclear grade of DCIS.

9.3.2 Kinetics

The kinetic pattern of DCIS varies widely. The initial enhancement phase is defined as occurring within the first 2 minutes after contrast injection or until peak enhancement is reached [39]. In the initial phase, the most common kinetic pattern for DCIS is a fast uptake, seen in 49–68 % of cases, less commonly an intermediate (<20 % of cases) or slow pattern (<20 % of cases) [36, 38, 46]. Of note, in the new BI-RADS 5th edition the term fast has replaced rapid [39]. The delayed enhancement phase is defined as following 2 minutes after contrast injection or after peak enhancement is reached and is used to described the shape of the curve [39]. There is a wide variety of delayed phase kinetic patterns seen in DCIS. The most common pattern is a plateau (type 2), seen in 20–52 % of cases (Fig. 9.8) followed by a washout pattern (type 3), in 28–44 % of cases, and persistent enhancement pattern is seen in 20–30 % of cases [36, 38, 46]. Given the significant variation in the kinetic patterns of DCIS,

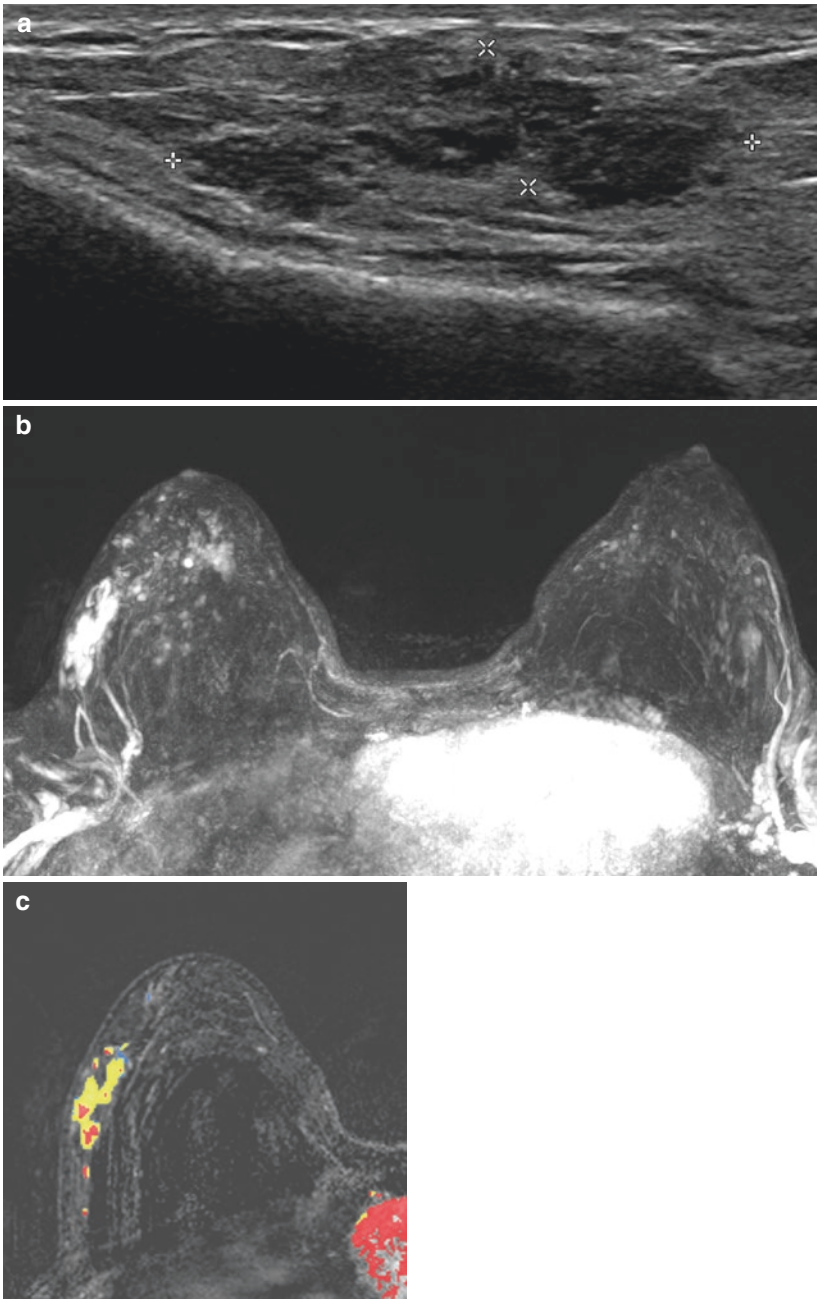

Fig. 9.8 High grade DCIS in a 56-year-old woman with a palpable lump (**a**) Ultrasound image demonstrates a hypoechoic mass with indistinct margins and echogenic foci, corresponding to calcifications on mammography. (**b**) MRI performed for extent of disease demonstrates corresponding segmental clumped NME (**c**) with predominantly Type 2 (plateau) delayed kinetic pattern, compatible with biopsy proven high grade DCIS (Kinetic key: *Blue* = type 1, *yellow* = type 2, *red* = type 3)

it is very important to base the assessment for DCIS on MRI primarily on morphology rather than kinetics.

Additional studies have looked at whether kinetic patterns may predict grade of DCIS. Jansen et al. found no significant difference in kinetic patterns, both initial and delayed, and grade of DCIS [36]. A study in 2012 by Rahbar et al. found no significant association between nuclear grade and delayed phase of enhancement. They did find a non-significant trend (p = .05) towards higher peak initial enhancement in high-grade DCIS lesions, compared to non-high grade, at 1.5 T [47]. However, a subsequent study by Rahbar et al. in 2015, found no statistically significant difference in kinetic patterns, initial and delayed, of various grades of DCIS when done at 3 T MR imaging [45].

9.3.3 1.5 T Versus 3 T

There has been increasing use of 3 T MRI for clinical dynamic contrast enhanced breast imaging over the last decade. As it has become apparent that high spatial resolution allows for more accurate detection of DCIS, it follows that 3 T MRI may have increased sensitivity for DCIS, as a benefit of 3 T imaging is higher signal to noise ratio, which allows for higher spatial resolution [48]. Rahbar et al. did a prospective study in patients newly diagnosed with pure DCIS. Each patient underwent a pre-operative breast MRI at both 1.5 T and 3 T imaging. They found that maximum DCIS lesion size on 3 T had a higher correlation with maximum size found on pathology than did 1.5 T [49]. 3 T may therefore be clinically helpful in pre-operative planning for DCIS lesions and further research in this area may be of clinical significance.

9.4 Diffusion Weighted Imaging

As discussed earlier, DCIS has a variable morphologic and kinetic presentation at MRI, which may present diagnostic challenges. No statistically significant difference in morphology has been shown to predict high grade versus non-high grade DCIS [36, 37, 45]. As the concerns for overdiagnosis and overtreatment grow, this becomes a challenge. In addition, another challenge is that breast MRI requires gadolinium administration with may limit accessibility. Diffusion weighted imaging (DWI) is a valuable MRI technique that may better be able to predict grade of DCIS and in addition it does not require any intravenous contrast. DWI quantifies the random motion of water in biologic tissue. The apparent diffusion coefficient (ADC) is the most common quantification of this water transport. Cancers are often more cellular than normal tissue, therefore restrict the diffusion of free water, and this forms the basis of DWI in oncology [50]. In breast cancer, a restricted ADC is widely accepted as a marker of cellularity [51–57].

Rahbar et al. looked at 74 pure DCIS lesions and found that quantitatively these lesions demonstrated higher DWI and lower ADC than normal tissue in the same

patient, with a statistical significant difference [58]. In a subsequent study Rahbar et al. studied whether 3 T MRI was able to identify low risk DCIS. This study looked at the features of 36 DCIS lesions on MRI, 8 classified as low risk and 28 high risk. Again no statistically significant differences were found for morphologic features and kinetics between low risk and high risk DCIS. However, low risk DCIS lesions showed different DWI features, such as higher contrast to noise ratio and lower normalized ADCs than high-risk DCIS lesions [45].

Iima et al. studied 22 patients with pure DCIS and found that the ADC of high and intermediate grade DCIS were significantly lower than those of low-grade DCIS, and there was a significant negative trend between mean ADC and tumor grade. These preliminary results suggest that possibly DWI may be able to identify patients with low grade DCIS, which if confirmed could decrease patient anxiety and decrease invasive approaches [59].

An additional study by Rahbar et al., suggests that the combination of findings on DCE MRI and DWI may be able to predict low grade from high grade DCIS, with up to 81% accuracy. Larger size lesions corresponded with higher grade DCIS. A higher contrast to noise ratio (CNR), between each lesion and normal tissue on DWI (b = 600 s/mm^2) was seen in non-high grade DCIS which was thought to be related to greater T2-shine through, as no significant difference in ADC values between high grade and non-high grade lesions [45]. This lack of difference between ADC values and grade of DCIS is different than the results of Iima et al., as ADC values are technique-dependent, and further research is required in this area.

9.5 MRI Features Suggestive of Occult Invasion

Microinvasive DCIS is a subtype of disease which shows 1 mm or less of extension of cancer cells through the basement membrane. Hahn et al. found that microinvasive DCIS showed more suspicious MR imaging characteristics than pure DCIS. These findings included spiculated mass-type lesion, segmental distribution, and clustered ring enhancement of nonmass enhancement, and strong initial enhancement kinetics with washout kinetics [60].

The early identification of an invasive cancer along with DCIS, which is different than microvinasive cancer, is important because it results in changes to surgical management, including a sentinel node biopsy [61]. Wisner et al. looked at whether certain MRI BI-RADS criteria or radiologist perception correlated with invasive cancer after initial diagnosis of DCIS on core-biopsy. 13/51 patients with core-biopsy proven DCIS had invasion at excision. There was a significant positive correlation between the presence of a mass and invasion while nonmass enhancement had a significant negative correlation with invasion [62]. Goto et al. found that that certain MR findings of breast lesions, particularly in NME lesions, including large size of lesion and relatively higher signal intensity on fat-saturated-T2 W images, were suggestive of invasion in biopsy proven DCIS [63]. However, Nori et al. did not find MRI morphologic features to be significantly associated with prediction of

DCIS plus invasive cancer when looking at cases of DCIS diagnosed on percutaneous biopsy [64]. This is an area where future research attention may be helpful.

9.6 Summary

With the advent of screening mammography the incidence of DCIS has increased significantly. MRI has been shown to be the most sensitive examination in the detection of DCIS. Not only is MR the most sensitive imaging modality but it is likely the one to detect the most clinically relevant cases of DCIS, and it is therefore essential to recognize the various presentations of DCIS on MR imaging. The most common morphology of DCIS is nonmass enhancement, and the most common distribution for the NME is in a segmental pattern. The most common kinetic pattern of DCIS is a fast initial uptake, however there is great variation in the delayed phase. It is thus, essential to evaluate lesions based on the morphologic pattern.

Given the broad spectrum of disease that DCIS represents, and the significant current controversies regarding both overdiagnosis and overtreatment of DCIS, additional research evaluating MR and its various techniques, including DWI, may be extremely useful in helping increase the detection of clinically relevant cases of DCIS and improving prediction of nonprogressive DCIS.

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