Multimodality Imaging of Ductal Carcinoma In Situ

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Abstract

Purpose of Review We aim to review the appearance of ductal carcinoma in situ (DCIS) across the spectrum of imaging modalities used in common clinical practice.

Recent Findings Changes in technology and clinical breast cancer screening patterns have impacted the imaging evaluation of DCIS. DCIS classically presents as asymptomatic calcifications in women undergoing screening mammography. The replacement of traditional 2D mammography with digital breast tomosynthesis has changed the typical appearance of screen-detected DCIS. Ultrasound is traditionally utilized to detect DCIS in women with clinical symptoms, but efforts to increase screening ultrasound rates for women with dense breasts makes it more important to identify the appearance of DCIS in asymptomatic women. Improvements in MRI technology have made MRI the most sensitive imaging modality to detect DCIS and define the extent of disease, which is increasingly important given greater utilization of MRI for high-risk screening and determination of extent of known disease. Finally, the emergence of active surveillance, or non-surgical management, for DCIS has increased the focus on presurgical identification of associated invasive cancer, with early results demonstrating promise via computer vision and deep learning approaches for this task.

Summary DCIS has a highly variable imaging appearance which is subject to changes in imaging technology and clinical management.

Keywords Ductal carcinoma in situ · Mammography · Ultrasound · MRI · Digital breast tomosynthesis · Radiology

Introduction

Ductal carcinoma in situ (DCIS) is a non-invasive stage 0 form of breast cancer [1]. DCIS classically presents as an asymptomatic incidental finding and the widespread adoption of organized screening mammography has resulted in a steady increase in the incidence of DCIS [2]. Although DCIS has been well-described in the literature over the last several decades, recent changes to clinical practice and imaging technology have shifted the focus of DCIS imaging. First, the rapid adoption of digital breast tomosynthesis (DBT), also referred to as 3D mammography, requires an understanding of the key similarities and differences in the appearance of DCIS on DBT from traditional 2D mammography. Second, recognizing the appearance of DCIS on ultrasound (US) is increasingly important due to widespread advocacy efforts and state legislation regarding supplemental ultrasound for women with dense breasts [3]. Third, new high-risk screening guidelines recommend annual MRI, which increases the population of women undergoing screening MRI [4]. Finally, ongoing clinical trials are exploring the feasibility of non-surgical treatment of DCIS, termed active surveillance. Safe enrollment in active surveillance requires differentiation of DCIS from invasive disease in the presurgical setting, which is a relatively novel task for radiologists. It is therefore important to have a comprehensive understanding of the multimodality appearance of DCIS.

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Mammographic Appearance of DCIS

With the implementation of screening mammography, the incidence of DCIS has increased significantly and now accounts for approximately 25% of breast cancers in the USA [5]. Furthermore, improved mammographic technology and standards for reporting have resulted in mammographic sensitivity of 87–95% for the evaluation of DCIS (Table 1) [5]. DCIS most commonly (~ 75%) presents as asymptomatic calcifications on screening mammography (Fig. 1) and less often as a mass or architectural distortion (Fig. 2) [6]. In cases of symptomatic DCIS, the most common presentation is either a palpable lump or nipple discharge.

The underlying mechanisms responsible for the presence of associated calcifications in DCIS are not well established. Calcifications comprised of calcium oxalate (type I) are generally associated with benign non-DCIS pathology while those composed of calcium hydroxyapatite (type II) are more typical for DCIS [7]. Modeling based on physiologic bone mineralization has given insights into how these pathologic microcalcifications may be formed [8]. It is hypothesized that physiologic bone matrix proteins are expressed in mammary cells and demonstrate altered expression in the tumor microenvironment. For example, the phosphoprotein OPN responsible for regulating mineralization is abundant in bone but is also known to be expressed in breast cancer and associated with a worse prognosis. Nonetheless, even though mammographic calcifications have been evaluated for decades, our understanding of their genesis and clinical relevance remains an area of active investigation.

DCIS microcalcifications typically present with a suspicious morphology and/or distribution defined by the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Atlas [9•]. The suspicious morphology descriptors in order of likelihood of malignancy are coarse heterogeneous (13%), amorphous (21%), fine pleomorphic (29%), and fine linear or fine-linear branching (70%) [9•]. In rare cases, typically benign morphologies, such as round, can be found with DCIS, but these are usually low grade cases without comedonecrosis [6]. The distribution of microcalcifications is also associated with the likelihood of malignancy: diffuse (0%), regional (26%), grouped (31%),
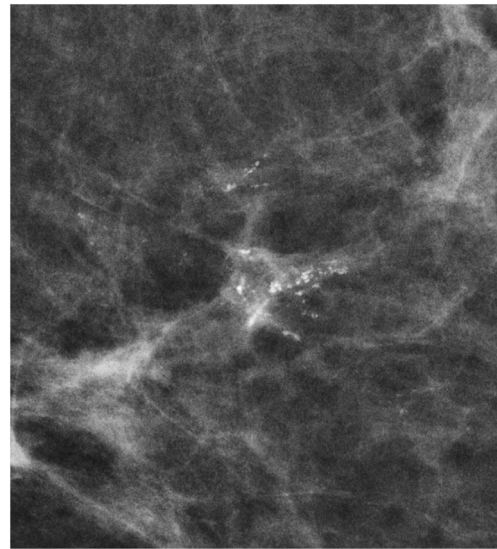

Fig. 1 Classic appearance of DCIS as pleomorphic, grouped calcifications seen incidentally on screening mammography

linear (60%), and segmental (62%) [9•]. However, the utilization of these morphology and distribution descriptors is not evenly distributed and the majority of DCIS cases present as grouped pleomorphic calcifications [10]. Due to the notable inter- and intra-observer variability in the use of these BI-RADS descriptors, it is less important which suspicious descriptors are used, but rather to differentiate between the definitively benign and suspicious descriptors [11].

Microcalcifications may also provide prognostic information. DCIS is a heterogeneous disease process with discrete nuclear grades, varying levels of cellular differentiation, and potential comedonecrosis, all of which can affect the biology of the disease [5]. Several studies have linked microcalcifications demonstrating linear branching, coarse heterogeneous, and fine pleomorphic morphologies with an increased risk of local recurrence [10, 12, 13]. These morphologies are also associated with higher nuclear grade and
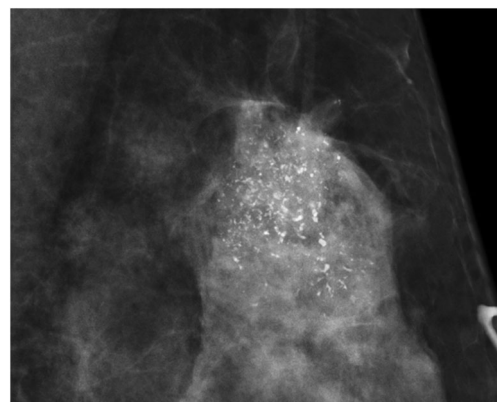
Table 1 Comparison of mammography and MRI sensitivity based on nuclear grade. Adapted from [43••]

DCIS	Mammography	MRI
All	56% (47–63%)	92% (86–95%)
Low grade	61% (45–75%)	80% (64–90%)
Intermediate grade	59% (41–75%)	91% (75–98%)
High grade	52% (41–62%)	98% (91–100%)

Data refer to sensitivity with 95% confidence intervals

Fig. 2 DCIS less commonly presents as a palpable mass on mammography, but calcifications are still frequently present. The associated mass may be due to distention of the duct or the development of an associated invasive component

comedonecrosis [10, 14]. Comedonecrosis is thought to demonstrate a greater invasive potential and proliferation rate indicating a more aggressive biology [15]. However, due to the significant overlap in mammographic appearance of different histological grades, the correlation between calcification morphology and histological grade may be somewhat variable [16, 17]. The number and extent of calcifications are also prognostic factors. Calcification numbers in excess of 20 correlate with higher nuclear grade and the presence of necrosis [6], while larger lesion size correlates with increased risk of occult microinvasion and multicentric disease [18].

Approximately one quarter of DCIS cases will present with an associated mass, asymmetry, or architectural distortion, either alone or in conjunction with calcifications [6, 19, 20]. These soft tissue components may represent distended and dilated ducts, periductal fibrosis, or elastosis. However, it may also represent associated invasive disease, as a mass or palpable abnormality increases the likelihood of upstaging to invasive disease at surgical excision [21••]. When DCIS does present as a soft tissue abnormality without calcifications, it is more likely to be grade 1 DCIS [6, 20]. Interestingly, the proportion of DCIS presenting as a soft tissue abnormality increases with age, which might reflect differences in DCIS biology or an obscuring of subtle masses in younger women with dense breasts [19, 22]. Finally, it is uncommon for DCIS to present as architectural distortion but this appearance is often found in association with sclerosing adenosis or radial scar with DCIS incidentally found in the adjacent Cooper's ligaments [23].

Digital Breast Tomosynthesis Appearance of DCIS

Digital breast tomosynthesis (DBT) is rapidly replacing traditional 2D mammography as the primary breast cancer screening modality. Given the improved ability of DBT to evaluate masses, asymmetries, and architectural distortion, especially in women with dense breasts, DBT offers improved detection for non-calcified DCIS [24]. Similarly, DBT allows for improved detection of associated soft tissue abnormalities in cases of calcified DCIS, which may signify an underlying invasive disease component [25]. For calcified DCIS, the performance depends on whether DBT is performed in conjunction with mammography or whether synthetic mammograms (SM) generated from the tomosynthesis images are used. DBT plus mammography requires approximately double the radiation dose and multiple studies have shown that cancer detection rates are comparable whether traditional mammography or SM is used in conjunction with DBT [26, 27]. As a result, DBT is increasingly being performed alone with SM as a replacement for mammography.

SM are generated by vendor-specific proprietary algorithms created from the individual low-dose tomosynthesis acquisitions but this process changes the appearance of DCIS calcifications via the accentuation algorithms utilized to make abnormalities appear more conspicuous [28, 29••]. In general, SM offers comparable performance to traditional mammography for the detection of calcifications and to define their extent, although published series are conflicted [30–33]. However, the morphology of calcifications on SM can be distorted such that BI-RADS descriptors to differentiate benign from suspicious calcifications cannot be adequately assessed (Fig. 3). As a result, DCIS calcifications may be incorrectly dismissed as benign on SM and it is best practice to obtain additional standard 2D views, particularly magnification views, for any new calcifications.
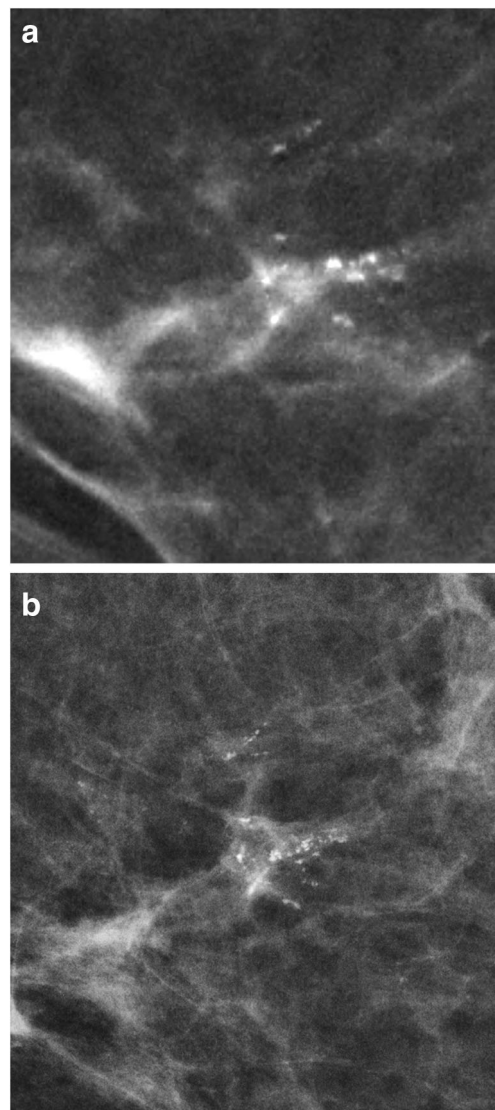

Fig. 3 The morphology of calcifications on synthetic mammograms generated from digital breast tomosynthesis (**a**) is different from traditional 2D mammography (**b**)

Ultrasound Appearance of DCIS

While DCIS is most commonly identified through the presence of microcalcifications on mammography, ultrasound may be helpful in the detection of non-calcified DCIS and for further characterization of mammographic and MRI findings.

Non-calcified DCIS, often presenting as a mass or asymmetry, is thought to represent between 2 and 23% of DCIS cases [19, 34, 35••]. Clinical scenarios may include nipple discharge, abnormality detected at screening ultrasound, or a mammographically occult palpable lesion. The findings of non-calcified DCIS on ultrasound are heterogeneous—mass, ductal changes, distortion, cluster of cysts, vague hypoechoic area—with mass being the most commonly reported abnormality of those visible on ultrasound (Fig. 4) [20]. Masses may be somewhat benign in appearance with oval shape and circumscribed or indistinct margins with parallel orientation though also can be irregularly shaped with non-circumscribed, frequently microlobulated margins, and internal vascularity [19, 34, 36]. The presence of internal vascularity may be seen in up to 50% of masses and may heighten suspicion for malignancy when evaluating lesions [35••]. Ductal extension may be absent. A "pseudomicrocystic" appearance is a non-BI-RADS descriptor that has been coined for DCIS that
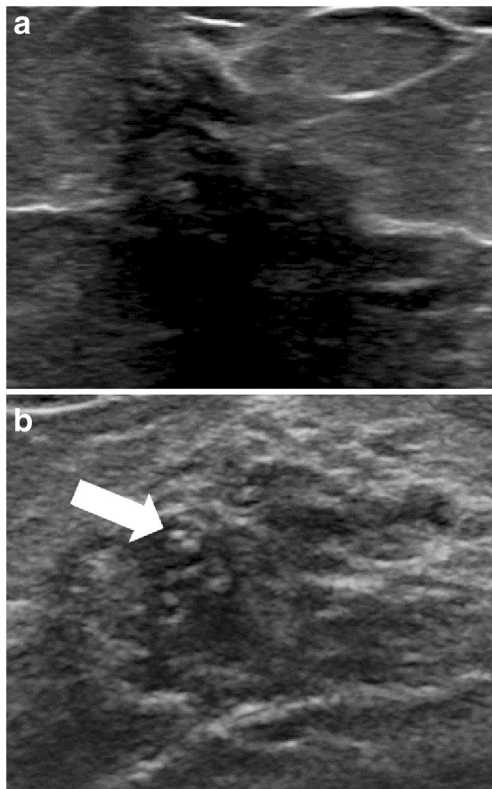
Fig. 4 The ultrasound appearance of DCIS is highly variable but will most commonly be hypoechoic with an irregular shape and indistinct margins (**a**). If sufficiently large, microcalcifications may be seen on ultrasound as hyperechoic foci (arrow, **b**)

appears as a predominantly cystic lesion with solid components [37•]. Ductal changes including abnormal duct enlargement and ducts with solid filling defects, without associated microcalcifications, can be seen with non-calcified DCIS.

DCIS may often be found in conjunction with other benign or high-risk pathologies and there is significant overlap in the appearance of DCIS and sclerosing adenosis, apocrine metaplasia, atypical ductal hyperplasia, intraductal papilloma, fibrocystic change, and secretory changes. When associated with an intraductal papilloma (Fig. 5) or radial scar, DCIS may present on ultrasound as a vague area of shadowing due to underlying desmoplastic reaction. Recent literature suggests that a significant portion of non-calcified DCIS presents sonographically as a vague hypoechoic area [36]. This reflects the more typical appearance of DCIS on MRI as a focal or segmental area of enhancement, rather than a discrete mass. When DCIS (non-calcified) is identified on screening ultrasound, it is associated with favorable prognostic factors including lower nuclear grade, smaller tumor size, less comedonecrosis, and more hormone receptor positivity, compared to mammographically detected calcified DCIS [38].

In the evaluation of calcified DCIS, ultrasound is typically used to further evaluate a mammographically apparent soft tissue component or to facilitate biopsy planning when a stereotactic biopsy is not feasible. Ultrasound may be able to visualize 23–45% of calcifications seen at mammography [39, 40], with one study reporting minimum detected size at 0.5 cm [35••]. The ultrasound appearance of calcifications includes echogenic foci within a mass or duct and less commonly echogenic foci without a hypoechoic area or duct changes. Associated masses are often irregularly shaped and mildly hypoechoic with indistinct or microlobulated borders and may demonstrate ductal extension due to spread along ducts [37•, 41]. Mammographic features of calcifications that facilitate
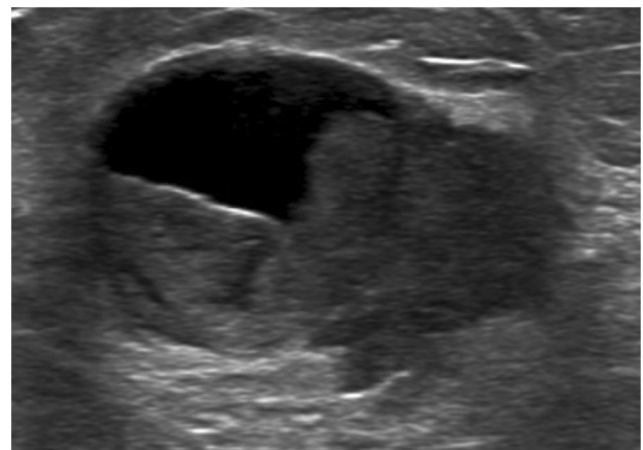
Fig. 5 DCIS may be found incidentally in association with other pathologic processes which may dictate the US appearance. The US image demonstrates an intraductal mass due to a papillary lesion with associated DCIS. This appearance is more classic for a papilloma than for DCIS

ultrasound detection are extent of calcifications greater than 1 cm and segmental distribution [42]. Calcifications that are visible on ultrasound have a higher likelihood of being malignant compared to those not seen and when associated with a mass more likely to have an invasive component [42].

MRI Appearance of DCIS

Historically, DCIS detection with MRI was associated with high false-negative rates because of MRI's inability to depict characteristic microcalcifications. With improvements in breast MRI spatial resolution over the past two decades, a distinct MRI abnormality, non-mass enhancement (NME), was found to commonly represent DCIS lesions. Upon integration of NME into the ACR BI-RADS lexicon, subsequent studies showed that MRI is in fact superior to mammography for DCIS identification, with particularly high sensitivity for high-grade lesions (Table 1) [43••, 44]. MRI is not only the most sensitive modality for identifying DCIS but also superior in extent of disease determination for treatment planning as shown by separate studies (Fig. 6) [45–47]. One study demonstrated that MRI estimated the correct size of DCIS to within 5 mm in 60% of cases compared to only 38% of cases for mammography [46]. Higher spatial resolution acquisitions achievable with 3 T systems are potentially providing even more accurate disease estimations [48•, 49].

On MRI, 60–80% of DCIS is described as segmentally or linearly distributed NME with clumped internal enhancement morphology (Fig. 7) [50–52]. NME is defined on MRI as an area of suspicious fibroglandular tissue enhancement that is not a mass (i.e., not space-occupying and no convex margins) and is of sufficient size that it would not be characterized as a focus (i.e., typically larger than 5 mm). Biologically, DCIS begins with intraductal tumor angiogenesis and proliferates locally through the breast ductal pathway recruiting abnormal periductal or stromal vascularity, which likely explains this unique enhancement pattern [5, 53]. Indeed, a mouse model suggests that DCIS enhancement is in part from the gadolinium contrast traveling across the milk duct basement membrane and collecting in the breast ducts, where DCIS resides [54]. This likely explains why linear (corresponding to a single duct) or segmental (triangular or conical with apex directed toward the nipple) distributions of NME are most commonly associated with DCIS pathology. In terms of NME internal enhancement, clumped (aggregates of small areas of enhancement forming a "cobblestone" pattern) is most often seen in DCIS, but clustered ring (thin rings of enhancement surrounding ducts, clustered together), a newer BI-RADS descriptor, is increasingly associated with DCIS and likely represents gadolinium accumulating peri- and intra-ductally (Fig. 8) [55, 56]. DCIS lesions less commonly present as masses or foci, where the growth pattern is more expansile. Local expansion

thought to be a more indolent growth pattern and corresponds with several studies which have shown that DCIS presenting as foci [57] or masses [58, 59] rather than calcifications are more often associated with lower grade disease.

While NME is the most common MRI presentation of DCIS, it is not specific for DCIS since benign proliferative pathology, including fibrocystic changes and pseudoangiomatous stromal hyperplasia (PASH), invasive breast cancer (ductal more common than lobular), and even normal breast tissue, can all present as NME. On dynamic contrast enhancement (DCE) MRI, DCIS exhibits variable kinetic enhancement features, with only a minority (28–44% of cases) of DCIS exhibiting the typical malignant kinetic profile of fast initial phase (signal increase of at least 100%) and washout on delayed phase (subsequent signal decrease of at least 10%) [5, 50]. Thus, since there are generally no morphologic or kinetic features of sufficient negative predictive value to obviate the need for biopsy, most NME lesions identified on MRI should be sampled rather than observed. Furthermore,
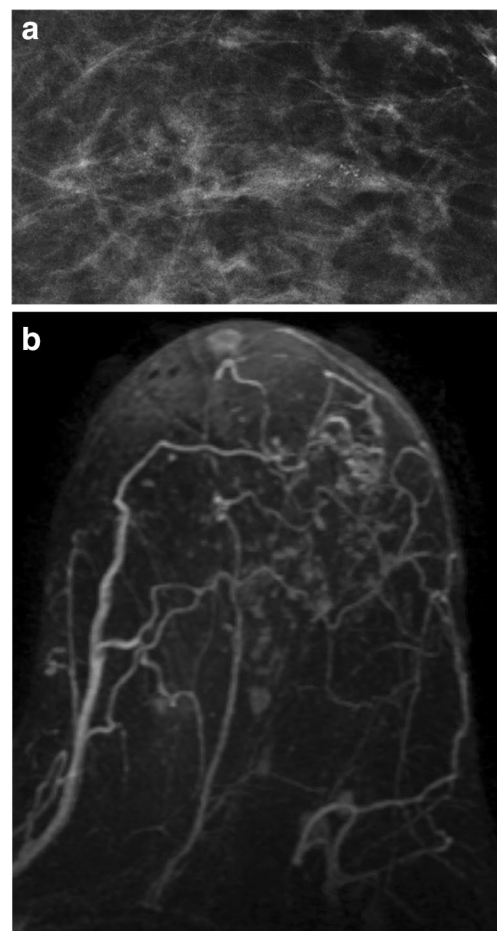

Fig. 6 MRI is better able to define the true extent of DCIS than mammography. Biopsy confirmed DCIS corresponds to 2 cm of amorphous calcifications on mammography (**a**) but 6.3 cm of clumped non-mass enhancement on MRI (**b**)
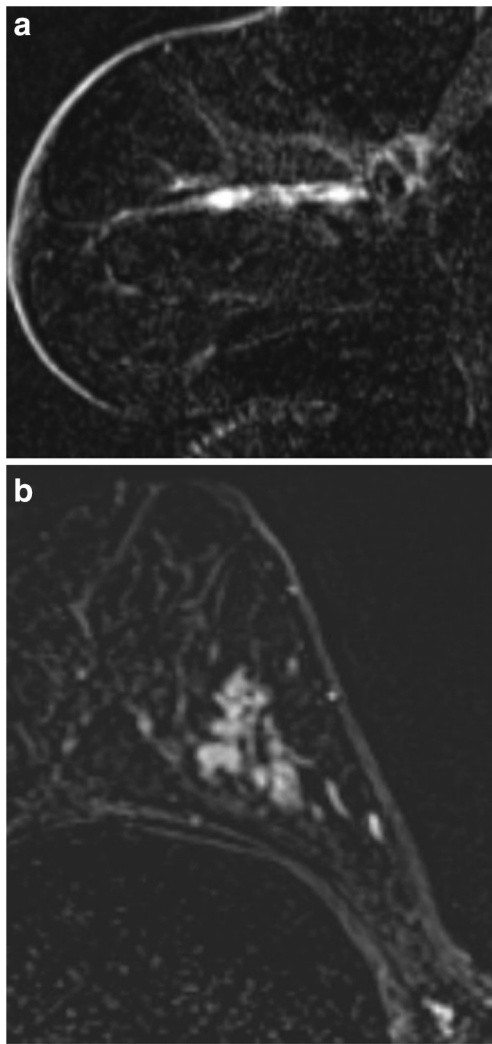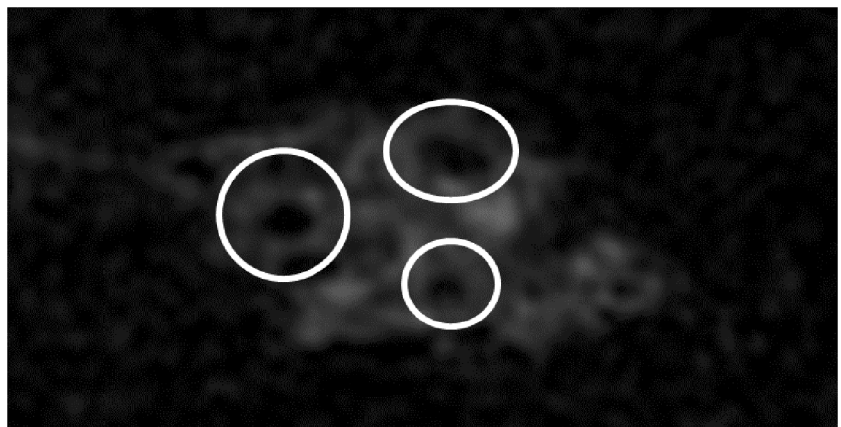
Fig. 7 DCIS most commonly presents as clumped non-mass enhancement on MRI, in either a linear (**a**) or segmental (**b**) distribution

when NME is identified on MRI performed to evaluate the extent of a known breast cancer, it is essential the NME is sampled under image guidance rather than simply

incorporated in the primary surgical so that unnecessarily extensive surgeries prompted by breast MRI are avoided.

While it is well established that MRI has exceptional sensitivity for DCIS detection, its clinical role remains controversial. For newly diagnosed DCIS by conventional imaging, disagreements remain regarding the value of preoperative MRI to improve surgical outcomes. Many have raised concerns that MRI leads to unnecessary mastectomies without a clear operative advantage, although it should be noted that most of the historical studies evaluating its use have been relatively small and retrospective in nature [60]. A recently completed prospective single arm multi-center trial (ECOG-ACRIN 4112) demonstrated that MRI accounts for a minority of conversions to mastectomy with most mastectomies performed due to patient preference, genetic testing outcomes, or positive margins on breast conservation surgery (BCS) [61•]. Furthermore, this trial demonstrated a very high rate (96.1%) of successful BCS for women who had wide local excision performed after MRI, which was corroborated by a recently published retrospective study by Lam and colleagues [62]. However, a small randomized trial of preoperative MRI failed to show a significant reduction in DCIS reoperation rates in the MRI-arm based on intention-to-treat analysis, although MRI did demonstrate a significant surgical benefit in the per-protocol analysis [63].

While the immediate surgical value of MRI to evaluate DCIS remains controversial, MRI may hold its greatest merit in facilitating individualized treatments [64]. Currently, the majority of DCIS lesions are likely overtreated with either excessive surgery, radiation, or medical therapy. Although MRI is superior for high-grade DCIS detection, its strength in assisting with treatment de-escalation remains largely unexplored. The aforementioned ECOG-ACRIN 4112 trial demonstrated a high level of patient acceptance for MRI in conjunction with a 12 gene assay (Onco*type* DX-DCIS) to determine the need for radiation therapy [61•]. Additionally, smaller individual studies have demonstrated the intriguing potential of approaches using MRI radiomics to predict DCIS biology and recurrence likelihood [65, 66]. The future direction of

Fig. 8 The clustered ring pattern of enhancement (circled) is a new descriptor for non-mass enhancement on MRI that is often associated with DCIS

MRI research should not only evaluate short-term surgical outcomes but also determine meaningful long-term outcomes, such as breast cancer recurrence and survival rates.

Active Surveillance for DCIS

Active surveillance is an alternative management strategy for DCIS that avoids surgical excision for select women with LOw Risk DCIS in order to address issues of overdiagnosis and overtreatment associated with the current standard of care surgical excision approach [67, 68].

There are currently three randomized prospective active surveillance trials in progress: The Comparison of Operation versus Monitoring with or without Endocrine Therapy for LOw Risk DCIS trial (COMET) in the USA [69], the LOw Risk DCIS trial (LORIS) in the UK [70], and the Management of LOw Risk DCIS trial (LORD) in the Netherlands [71]. Although the inclusion and exclusion criteria differ slightly between the trials, the success of active surveillance as a management strategy for DCIS requires improved methods to identify associated invasive disease at the time of initial diagnosis as these women

Fig. 9 DCIS is more likely to be upstaged to invasive disease when there is an associated palpable abnormality (a) or visible mass (b)

will not have surgical excision and undetected invasive disease could grow and metastasize.

The average upstaging rate of DCIS to invasive cancer at surgical excision is approximately 25% according to a large meta-analysis published in 2011, with several radiological (e.g., mass), clinical (e.g., symptomatic), and pathological (e.g., high nuclear grade) factors associated with higher upstaging rates (Fig. 9) [21••]. The application of multiple risk factors can reduce the upstaging rate to as low as 10%, but further efforts are needed to maximize the safety of active surveillance [21••, 72, 73]. Radiologists are not trained to differentiate DCIS from invasive disease as it is not currently a routine part of clinical focus for breast imagers, and research efforts have demonstrated that radiologists are only moderately successful at this task [74, 75••]. Changes to routine DCIS workflows to include ultrasound and MRI to evaluate for potential invasive disease may be needed for women eligible for active surveillance, while being mindful that additional imaging could increase the extent of intervention. Furthermore, different imaging modalities may be evaluating different aspects of DCIS, as exemplified by the CALGB 40903 trial which demonstrated that women with estrogen receptor positive DCIS treated with endocrine therapy had a decrease in tumor size on MRI but no appreciable change in size was noted on mammography [76]. The use of image analytics via computer derived features as well as deep learning features applied to both mammography and MRI have demonstrated preliminary success [75••, 77, 78]. However, larger datasets are needed to test the utility of these approaches given the sample size demands of advanced quantitative image analysis. Ultimately, a combination of imaging, clinical, and pathological advances will likely prove to be the most successful at reducing upstaging rates for patients potentially eligible for an active surveillance approach.
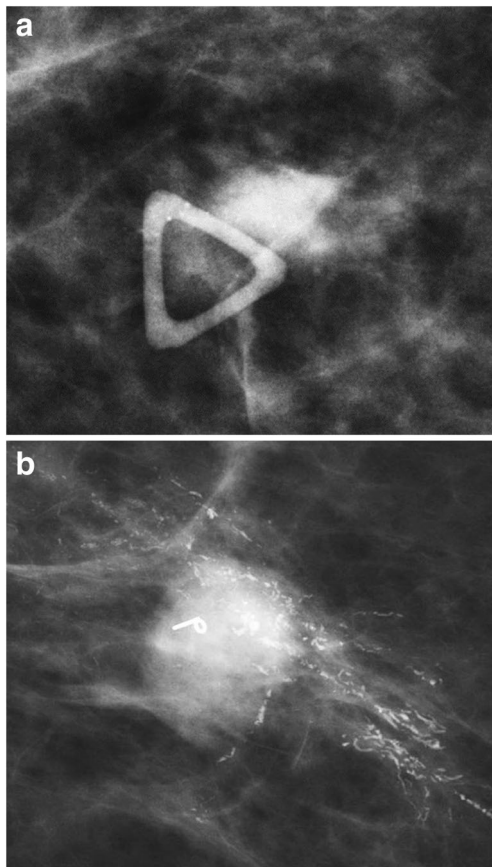
Conclusion

DCIS has a highly variable appearance on all imaging modalities. As technology improves, the relative strengths and weaknesses of each imaging modality will evolve for future evaluation of DCIS. Furthermore, changing clinical practice patterns, including screening ultrasound for women with dense breasts, high-risk screening MRI, and active surveillance will alter the most common clinical presentations of DCIS. Although mammography detects over 80% of DCIS, clinicians must recognize which imaging modality or combinations of imaging modalities to use in the appropriate clinical context for detection, evaluation, and surveillance of DCIS.

Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
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