Imaging of Ductal Carcinoma In Situ (DCIS)

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Contents

Abstract

The term ductal carcinoma in situ (DCIS) indicates a heterogeneous spectrum of disease with different prognosis and behavior. In most of the cases, DCIS is diagnosed in asymptomatic women during screening, though in some cases women might present with nipple discharge or a palpable mass. Typically, DCIS presents on mammography as microcalcifications with or without an associated mass or architectural distortion. Digital breast tomosynthesis has limited additional value for the evaluation of microcalcifications, but it can help in the identification and characterization

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of the concomitant soft-tissue modifications. DCIS is rarely primarily detected on ultrasound, though in some cases it might present as mass or with ductal abnormalities. Contrast-enhanced magnetic resonance imaging (MRI) is playing an increasingly relevant role in the diagnosis and management of DCIS. MRI has a higher sensitivity than mammography for DCIS, as it is able to identify also noncalcified lesions, and can more accurately assess the extent of disease. Whether this same role could be true for contrast-enhanced mammography as well is not yet established.

1 Background

Ductal carcinoma in situ (DCIS) is defined as a neoplastic deregulation of epithelial cell proliferation within the breast ducts, typically affecting the whole terminal ductolobular unit. It does not permeate the basal membrane and is thus noninvasive (or in situ) (Ellis 2010). While many authors still consider DCIS as a precursor lesion in the development of invasive carcinoma, others have suggested that DCIS may have a direct possibility to progress and metastasize. This theory is supported by the evidence of DCIS-related breast cancer mortality and of a lacking statistical connection between successful local treatment—to avoid local recurrence—and mortality in case of primary DCIS (Ellis 2010; Barrio and Van Zee 2017; Narod and Sopik 2018; Thompson et al. 2018).

As all neoplastic lesions, DCIS represents a heterogeneous spectrum of disease. While some DCIS can progress and even cause death, others will never progress into a clinically manifest disease. In autopsy studies on women who died of other reasons than breast cancer, the prevalence of undiagnosed DCIS has been reported as being around 8.9% (0–14.7%) while the rate of previously undiagnosed invasive cancer was 1.3% (0–1.8%) (Duffy et al. 2003; Erbas et al. 2006). Studies on initially misdiagnosed DCIS suggest that 14–53% may progress to invasive breast cancer within 10–15 years (Erbas et al. 2006). In addition, 3% of all DCIS present with lymph node metastasis at diagnosis, and 1.5–22.5% of all DCIS will recur with an invasive component, though recurrence was also found to be correlated with resection margins (Narod and Sopik 2018). The risk of a DCIS progressing in an aggressive disease seems to be related to its grade, with high-grade tumors being associated with a worse prognosis (Buerger et al. 1999; Simpson et al. 2005). According to some authors, the more aggressive forms of DCIS are also characterized by multiple localization in the same lobe as well as aberrant branching and lobularization, defined as neoductgenesis (Tot 2005; Zhou et al. 2014). The identification of these patterns at imaging and pathology should help distinguish cancer aggressiveness and tailor therapy accordingly.

2 Diagnosis of DCIS

Imaging has played a central role in the understanding and management of DCIS. The diagnosis of DCIS increased significantly with the introduction of breast cancer screening programs, and about 20% of all cancers diagnosed when screening with mammography are DCIS (Duffy et al. 2005; Virnig et al. 2010; Siegel et al. 2018). In the majority of the cases, DCIS is asymptomatic but in approximately 20% of DCIS cases, patients may present with nipple discharge or a palpable lesion (Schouten van der Velden et al. 2006). As a majority of DCIS presents with microcalcifications, mammography plays a central role in the diagnosis of this entity (Virnig et al. 2010). With the improvement of ultrasound (US) technology, it became evident that some lesions present with associated soft-tissue alterations that can be detected by using US (Gwak et al. 2011; Jin et al. 2015). The introduction of contrast-enhanced magnetic resonance imaging (MRI) led to new insights into DCIS, in particular revealing that at least 10% and up to 40% of DCIS do not present with or as mammographic microcalcifications (Stomper et al. 1989; Kuhl et al. 2007), and that the identification of hypervascularization rather than microcalcifications

could help guiding the management of these lesions (Esserman et al. 2006; Kuhl et al. 2007).

2.1 Mammography and Digital Breast Tomosynthesis

The detection of microcalcifications and, consequently, the diagnosis of DCIS increased with the spread of screening programs for breast cancer and also with the transition from screen-film to digital mammography. Improvements in image quality led to an increase in cancer detection through better visualization of smaller calcification clusters (Pisano et al. 2005; Bluekens et al. 2012; Luiten et al. 2017). Currently, approximately 42–72% of DCIS are initially diagnosed as asymptomatic microcalcifications visible on mammography. DCIS is detected in approximately 1.5 per 1000 women screened and accounts for 20–25% of cancers detected at screening (Duffy et al. 2003; Luiten et al. 2017; Siegel et al. 2018). However, about one-third of all lesions detected by mammography are microcalcifications: thus, microcalcifications are a rather common finding, but not necessarily associated with breast cancer (Wilkinson et al. 2017).

To stratify the risk of malignancy in these lesions, the Breast Imaging-Reporting And Data System (BI-RADS) committee of the American College of Radiology (ACR) has suggested semantic descriptors that define morphology and distribution of mammographic microcalcifications and assist in risk stratification (D'Orsi et al. 2013).

The most characteristic features of DCIS on mammography are fine microcalcifications with linear, linear-branching, or pleomorphic morphology and a linear or segmental distribution (Fig. 1). Approximately 80–100% of microcalcifications presenting with these characteristics are associated with malignancy (Liberman et al. 1998; Kim et al. 2015). The fine linear microcalcifications in DCIS are usually thin, irregular, and discontinuous (D'Orsi 2010). DCIS can also appear as amorphous or coarse heterogeneous microcalcifications. Amorphous calcifications (Fig. 2) are hazy and less conspicuous in comparison to pleomorphic and coarse heterogeneous (D'Orsi 2010; D'Orsi et al. 2013) and might represent DCIS in up to 20% of the cases (Berg et al. 2001; Kim et al. 2015). Coarse heterogeneous microcalcifications are larger than amorphous and pleomorphic microcalcifications (Fig. 3) and are associated with malignancy in 12–20% of the cases (Bent et al. 2010; Kim et al. 2015, 2018). DCIS usually does not present with a diffuse distribution, but it can be characterized by a regional or clustered/grouped distribution. In these cases, the positive predictive value ranges between 8% and 15% (Bent et al. 2010; Kim et al. 2015, 2018).

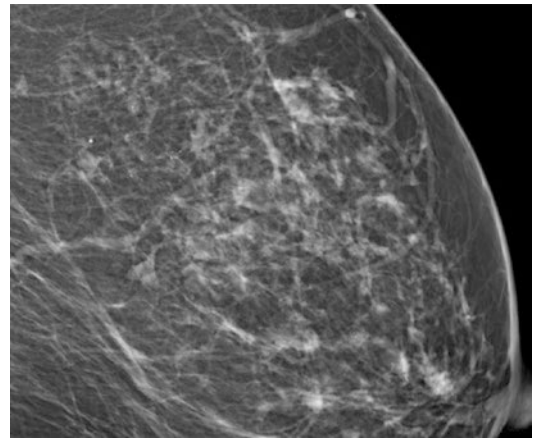

Fig. 1 Postmenopausal asymptomatic woman presenting with pleomorphic microcalcifications. Stereotactic vacuum-assisted breast biopsy revealed DCIS, G2, Her2/neu positive

While BI-RADS features indeed help stratifying the risk of underlying breast cancer, a meta-analysis has highlighted one major issue: there is practically no combination of BI-RADS features that does not exceed BI-RADS 3 benchmarks (Rominger et al. 2012). This implies that formally the vast majority of microcalcifications would require invasive workup, leading to a large amount of unnecessary biopsies for benign microcalcifications. Besides adverse effects of the minimal invasive biopsy procedure, the stereotactic biopsy procedure is technically demanding and expensive. Therefore, various alternatives have been proposed to manage suspicious microcalcifications classified as BI-RADS 3 and 4a. The option

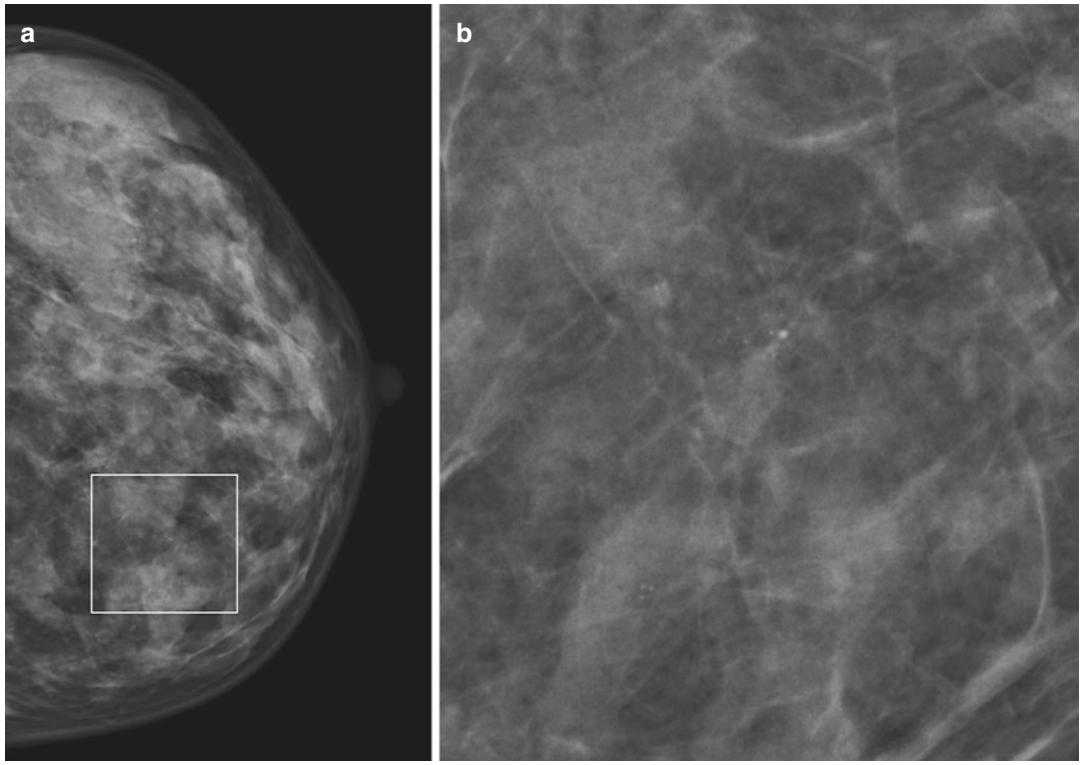

Fig. 2 Perimenopausal asymptomatic woman presenting with amorphous microcalcifications. Stereotactic vacuum-assisted breast biopsy revealed DCIS, G2, Her2/neu positive

of offering short-term follow-up is probably least favorable, as DCIS lesions may remain stable over years and unchanged imaging appearance does not exclude breast cancer (Coleman 2019). Additional tests, such as breast magnetic resonance imaging (MRI), can identify associated suspicious enhancement with a very high accuracy (see Sect. 2.3). The large-scale feasibility and cost-effectiveness of additional breast MRI examinations in this setting, though, remain unproven.

The role of digital breast tomosynthesis (DBT) for the diagnosis of DCIS is also limited. The majority of the studies showed that DBT increased the detection rate of invasive cancers, but not that of DCIS (Gilbert et al. 2015; Caumo et al. 2018; Skaane et al. 2019). This can be clearly explained by the technical characteristics of DBT: the reconstruction of quasi-3D images on the two mammographic views improves soft-tissue evaluation but does not add relevant information on the distribution or characteristics of microcalcifications. On the contrary, it might hinder the detection of small clusters of microcalcifications, though most studies agree that the performance of DBT and mammography to diagnose microcalcifications is comparable (Kopans et al. 2011; Clauser et al. 2015; Tagliafico and Houssami 2015). DBT can be helpful in detecting additional signs suggestive of malignancy, as the intraductal location of microcalcifications or the association with masses or architectural distortions, which might indicate the presence of associated invasive disease. DBT can also improve the detection of noncalcified DCIS and the evaluation of lesion extent (Fig. 4) (Berger et al. 2016; Su et al. 2017).

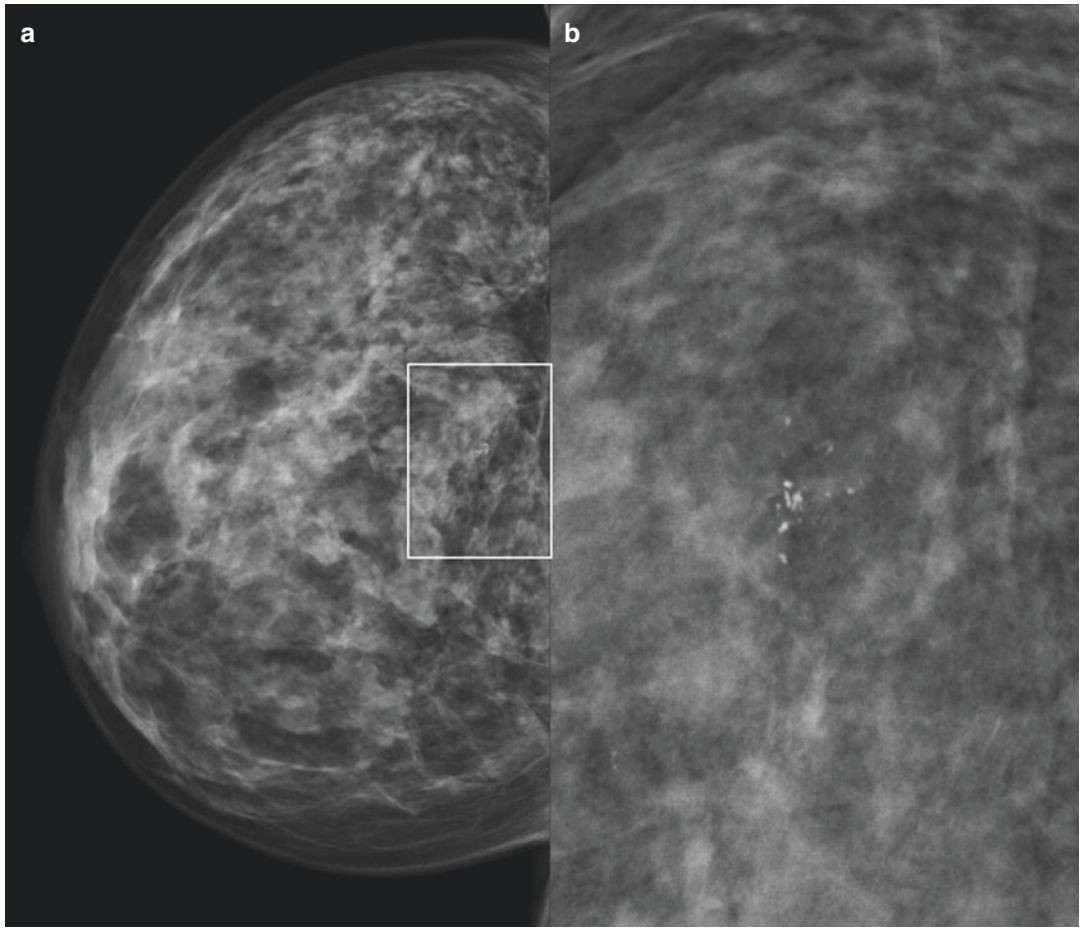

Fig. 3 Premenopausal asymptomatic woman presenting with coarse heterogeneous microcalcifications. Stereotactic vacuum-assisted breast biopsy revealed DCIS, G1, luminal A type

Synthetic mammography images, reconstructed from the DBT dataset, have been introduced as a method to avoid the increase in radiation dose due to the double acquisition of mammography and DBT. While the first studies indicated comparable results when using synthetic or digital mammography (Skaane et al. 2014; Bernardi et al. 2016; Clauser et al. 2016), further analyses suggested that the use of synthetic mammography does not provide the diagnostic performance achievable with combined mammography and DBT in screening (Caumo et al. 2017; Hofvind et al. 2019). In addition, microcalcifications might not be optimally visualized on synthetic mammography, and image characteristics vary between vendors (Nelson et al. 2016; Baldelli et al. 2018). Until more evidence is available, digital mammography remains the preferred examination technique to evaluate microcalcifications (Bae and Moon 2018).

2.2 Ultrasound

As DCIS usually presents with microcalcifications, the initial diagnosis of DCIS rarely occurs when using ultrasound.

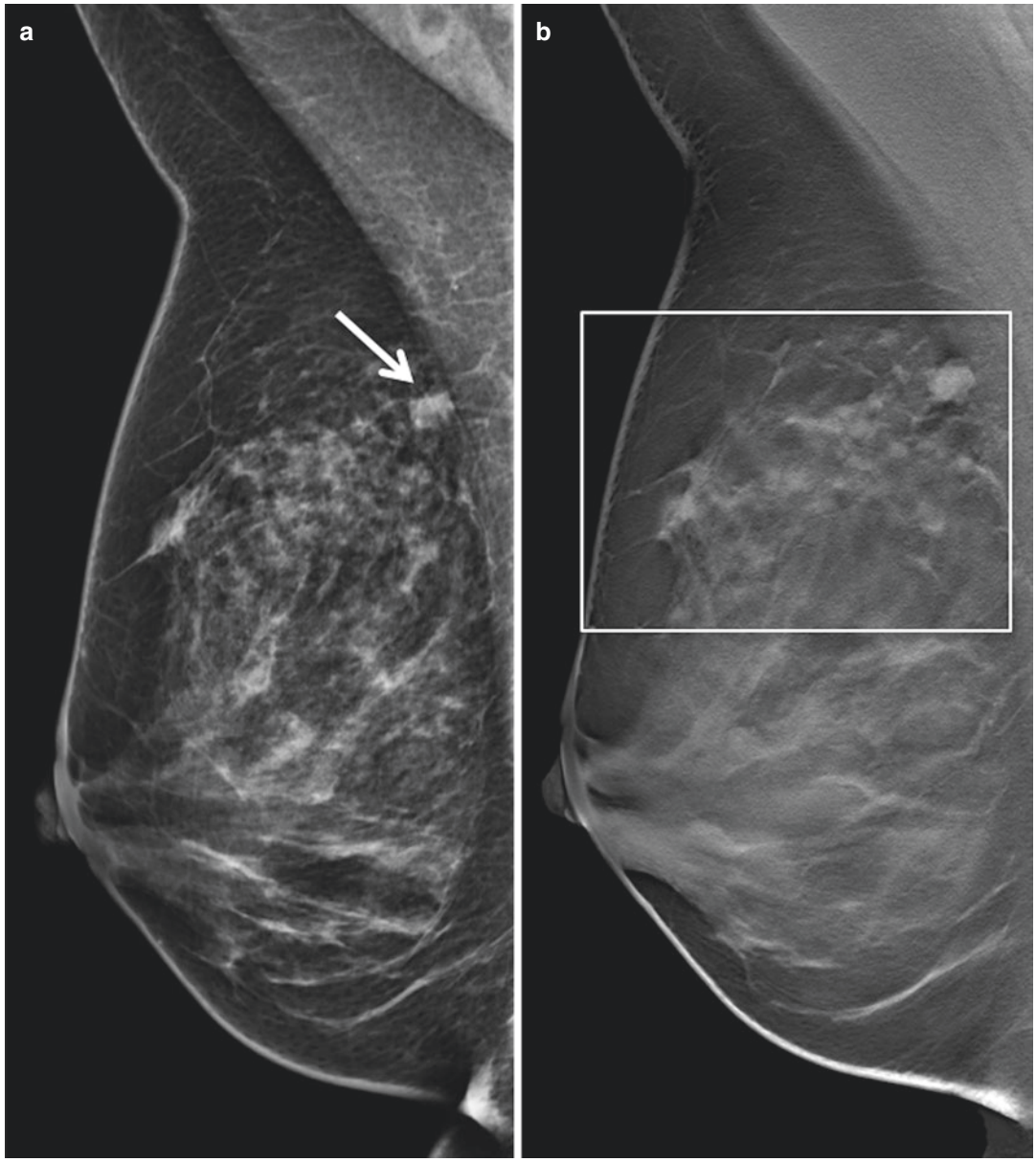

Fig. 4 Perimenopausal asymptomatic woman with a mammography detected mass (**a**). (**b**) The additional DBT identified the extensive associated architectural distortion, corresponding to DCIS, G2

If DCIS is visible on US, more than 50% of the findings appear as a hypoechoic mass lesion with indistinct margins, alone or with associated US-visible microcalcifications (Fig. 5). Other less common features, detected in 10–20% of the cases, can be microcalcifications alone or ductal abnormalities, in particular the identification of intraductal hypervascularized lesions, with or without microcalcifications (Londero et al. 2007; Scoggins et al. 2015). The presence of an US-visible lesion, as opposed to DCIS visible on mammography only, seems to be associated with a worse prognosis (Yoon et al. 2019).

Ultrasound can serve as image guidance for biopsy, when the lesion can be detected.

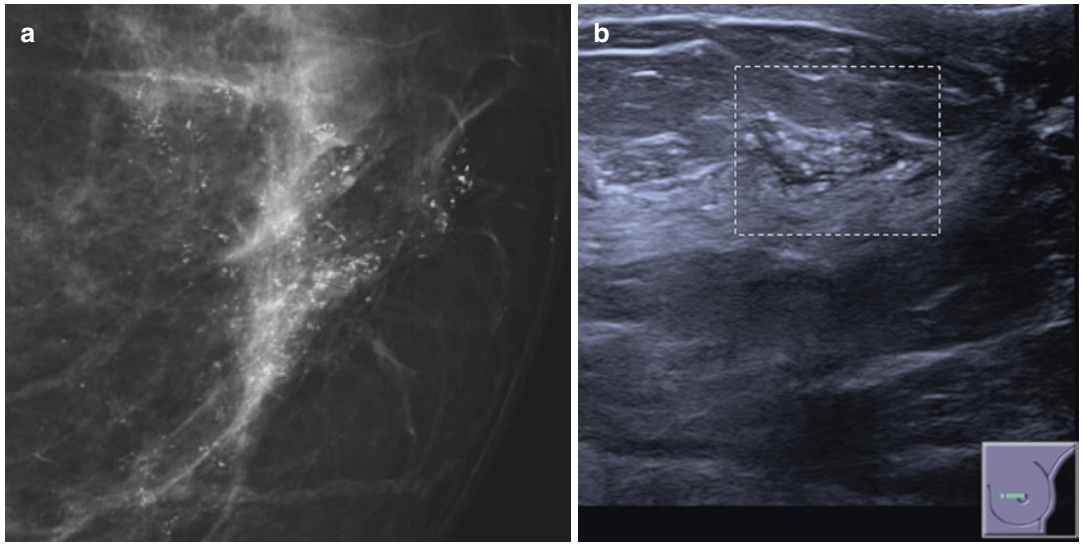

Fig. 5 Postmenopausal asymptomatic woman presenting with extensive pleomorphic microcalcifications on mammography (**a**). US (**b**) demonstrates an intraductal hypoechoic lesion (dashed margins) with evident hyperechoic calcifications. US-guided core needle biopsy revealed a calcified DCIS, G3

2.3 Contrast-Enhanced Breast Magnetic Resonance Imaging and Contrast-Enhanced Mammography

Breast MRI cannot directly visualize mammographic microcalcifications, but it is able to detect contrast enhancement associated with tumor growth and likely depict biologically active breast cancer (Kuhl 2009). Breast cancer growth leads to an increasing demand of nutrients that cannot be met by diffusion alone. The resulting lack of nutrients, including oxygen, leads to a hypoxia-induced and cytokine-mediated neovascularization, referred to as the angiogenetic switch. Consequently, biologically active neoplastic lesions enhance starting from about 2 to 3 mm in size (Jansen et al. 2009). Despite a regularly encountered opinion, this process not only is present in invasive cancer, but also affects all kinds of neoplastic growth including DCIS, lesions of uncertain malignant potential, and benign proliferations as well as inflammations. Consequently, a biologically active DCIS should present with contrast enhancement, whereas the absence of enhancement should allow to largely exclude an active neoplasm in case of mammographic microcalcifications.

MRI has been investigated by several studies as an additional examination technique to differentiate benign from malignant microcalcifications and avoid unnecessary biopsies. A meta-analysis investigating the use of contrast-enhanced breast MRI to diagnose malignancy in lesions presenting as mammographic microcalcifications reported a general negative predictive value of 90%, which increased to 99% when considering only the performance of breast MRI to exclude invasive cancers (Bennani-Baiti and Baltzer 2016; Baltzer et al. 2018). Despite the high negative predictive value, the best diagnostic criteria for the detection of malignancy in case of microcalcifications are still unclear. While the differentiation between presence and absence of enhancement may be the best predictor to exclude malignancy, its application would potentially yield a high rate of false-positive findings. Encouraging results regarding the application of the Kaiser score in lesions presenting as mammographic microcalcifications have recently been published (Wengert et al. 2019).

Diagnosis of malignancy, however, is not the only use of breast MRI in case of a diagnosed or

suspected DCIS. MRI can be able to better depict the extent of disease, particularly in women with dense breast parenchyma. In addition, it can better evaluate the involvement of the nipple as well as the distance from the skin, and thus help in pre-surgical planning (Balleyguier et al. 2019; Preibsch et al. 2019). The imaging characteristics of DCIS can be subtle, and a certain level of expertise for image interpretation and accurate preoperative evaluation is needed (Dietzel et al. 2017; Lam et al. 2019).

In the majority of the cases, DCIS presents as a non-mass enhancement (60–80%). The detection of a mass lesion is less frequent for pure DCIS lesions and can be seen in 14–40% of the cases. In less than 10% of the cases, DCIS presents at breast MRI as a focus (Greenwood et al. 2013; Dietzel et al. 2017).

When presenting as non-mass enhancement, DCIS is typically characterized by a linear or segmental distribution. The internal enhancement is usually heterogeneous or clumped: in particular in advanced cases, the more specific clustered ring pattern can be seen (Fig. 6).

The imaging characteristics of DCIS presenting as mass are variable but fulfill the criteria of malignancy (as given in Dietzel and Baltzer 2018): typically, the lesion presents with non-circumscribed margins and oval or round shape

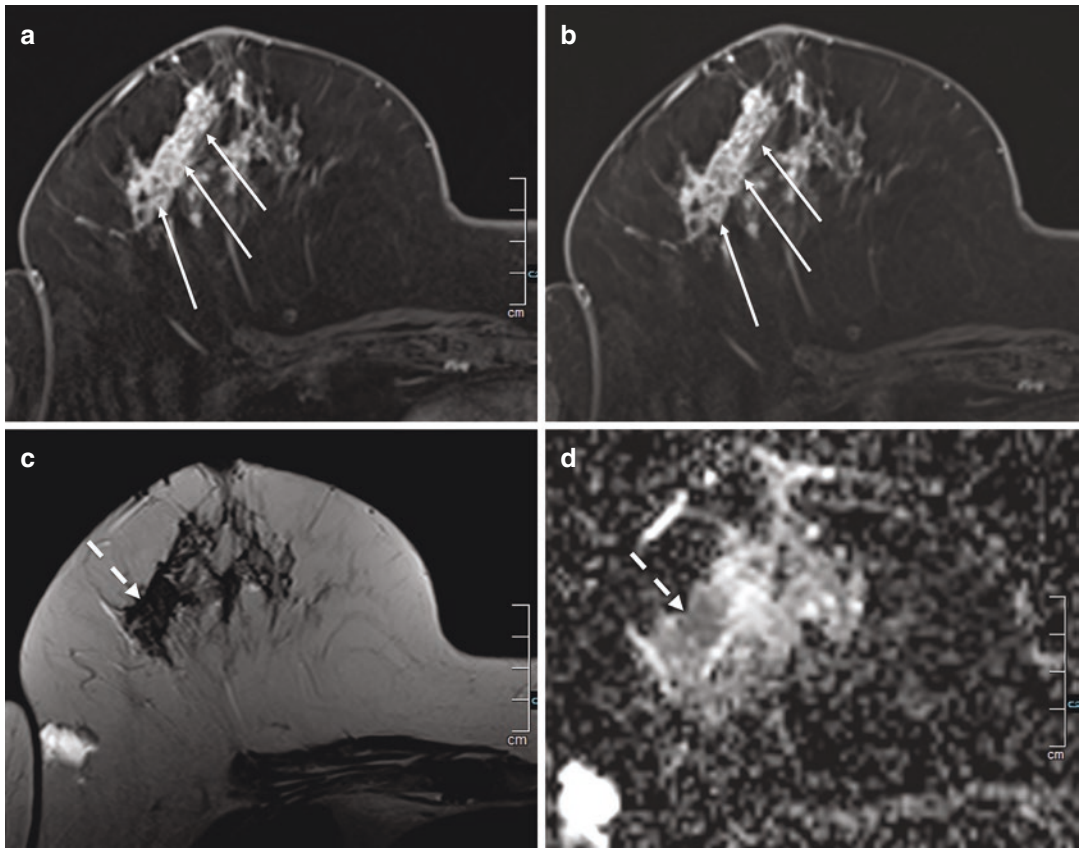

Fig. 6 Premenopausal asymptomatic woman with screen-detected parenchymal asymmetry and without definite lesion at US. Contrast-enhanced breast MRI (**a**: early enhanced, **b**: late enhanced, **c**: T2w-TSE, **d**: ADC map derived from diffusion-weighted-imaging) shows an early and distinct enhancement (**a**) with washout (loss of signal) in the late phase (**b**). The internal morphology of this non-mass enhancement is "clustered ring," a finding specific for DCIS. Note that both lesions correlated on T2w (**c**) and the ADC map (**d**) are hypointense, hinting at a biologically more aggressive lesion. Histology revealed DCIS G3, Her2/neu positive

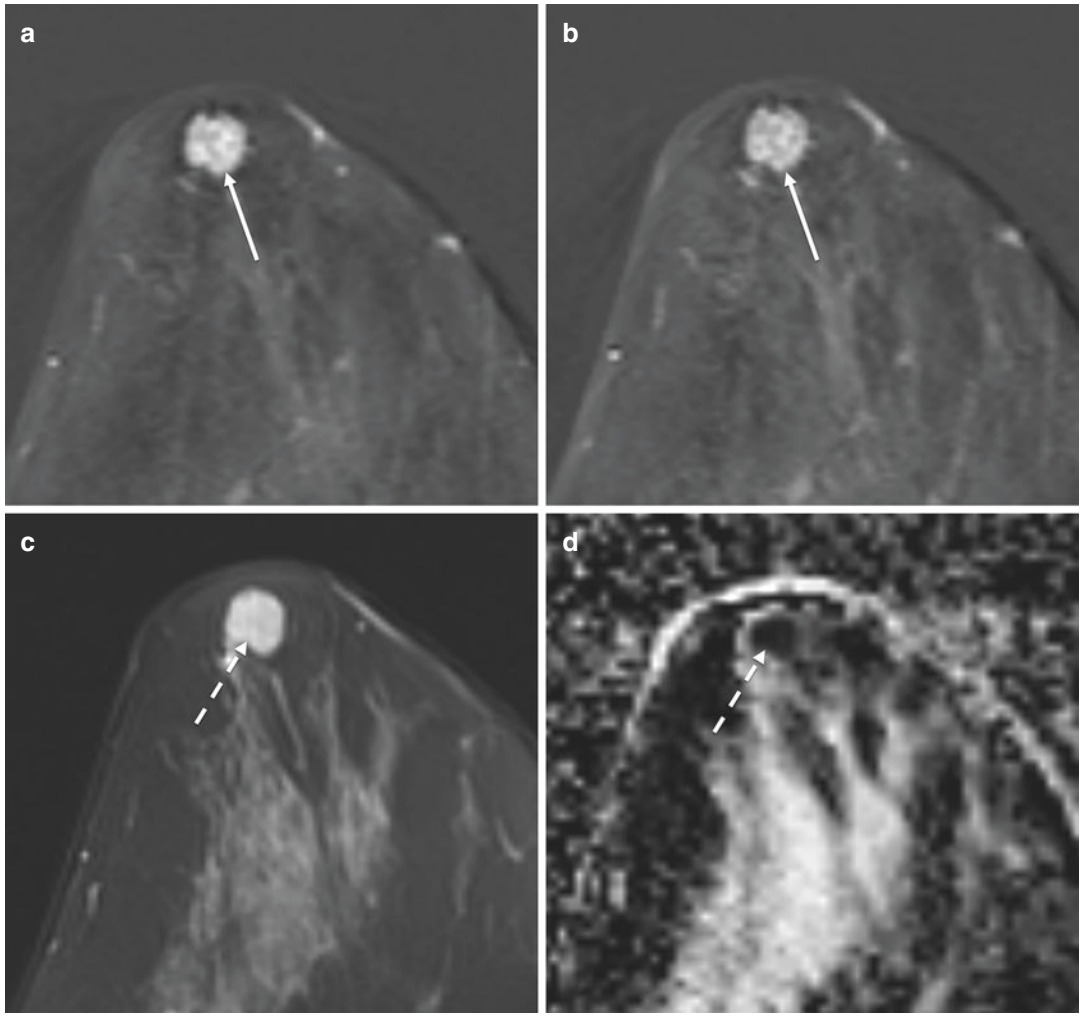

Fig. 7 Perimenopausal woman presenting with a new palpable lesion in the retroareolar region of the right breast. Contrast-enhanced breast MRI (**a**: early enhanced, **b**: late enhanced, **c**: T2w-STIR, **d**: ADC map derived from diffusion-weighted-imaging) shows a mass lesion (arrows) with non-circumscribed margins, washout in the late phase, and heterogeneous internal enhancement. STIR image shows high signal intensity (**c**), while the ADC map shows a low signal intensity (dashed arrows). US-guided core needle biopsy revealed a noncalcified DCIS, G1, luminal A type

(Fig. 7). Irregular masses with spiculated margins have also been described in the literature (Greenwood et al. 2013; Dietzel et al. 2017).

Not many studies evaluated the role of contrast-enhanced digital mammography (CEDM) for DCIS. As microcalcifications are clearly visible on CEDM, the additional value of CEDM compared to MRI could be the concomitant evaluation of both microcalcifications and associated contrast.

To date, only one small study analyzed the usefulness of CEDM for DCIS. The authors showed that not all pure DCIS showed a detectable enhancement on CEDM, while enhancement could be identified in lesions with microinvasion (Vignoli et al. 2019). The future adoption of CEDM in clinical practice, however, will largely depend on its ability to detect subtle lesions such as DCIS in order to match the superior sensitivity of MRI (Baltzer et al. 2017).

3 Comparative Sensitivity of Mammography and MRI

A number of studies have compared the sensitivity of mammography with that of MRI. Both methods can claim an advantage over the other: while MRI cannot visualize microcalcifications, mammography does not provide functional information. Advocators of MRI regularly point out that the functional information on tissue vascularization would rather detect biologically aggressive high-risk DCIS while mammography inherently tends to diagnose less aggressive, probably even biologically insignificant disease (Kuhl et al. 2007; Kuhl 2009). While it seems to be true that MRI has a higher sensitivity for detection of DCIS than mammography (Fig. 8), results are somewhat controversial as some studies report a higher sensitivity for DCIS using mammography as compared to MRI. A definite bias towards mammography-detected DCIS may be assumed as only mammography is used in national screening programs for imaging-based secondary prevention. This assumption is confirmed by the higher absolute and relative rates of DCIS in mammography-screened populations. While a negative contrast-enhanced MRI scan can indeed largely rule out (invasive) breast cancer, the hypothesis that only low-grade and low-risk DCIS are missed by breast MRI is not backed up by the current empirical evidence (Facius et al. 2007; Kuhl et al. 2007; Vag et al. 2008).

4 Risk Stratification in DCIS

When DCIS is diagnosed, two main factors have to be taken into consideration: the risk for this lesion to be high grade and thus associated with a worse prognosis, and the risk for this lesion to be associated with invasive cancer, requiring a more aggressive therapy including axillary lymph node sampling.

Mammography is of limited use in differentiating low- from high-grade lesions. Some studies suggested that DCIS presenting as linear-branching and casting-type calcifications as well as with an associated mass and larger lesion size are more often high-grade tumors (Dinkel et al. 2000; Barreau et al. 2005; Zhou et al. 2017). However, all these scarce reports showed a large overlap between lesion characteristics and grade, suggesting a limited role of mammography in this respect.

MRI seems to be the best tool for both detection of high-grade DCIS and identification of previously missed invasive cancers associated with DCIS lesions. Low-grade, estrogen receptor-

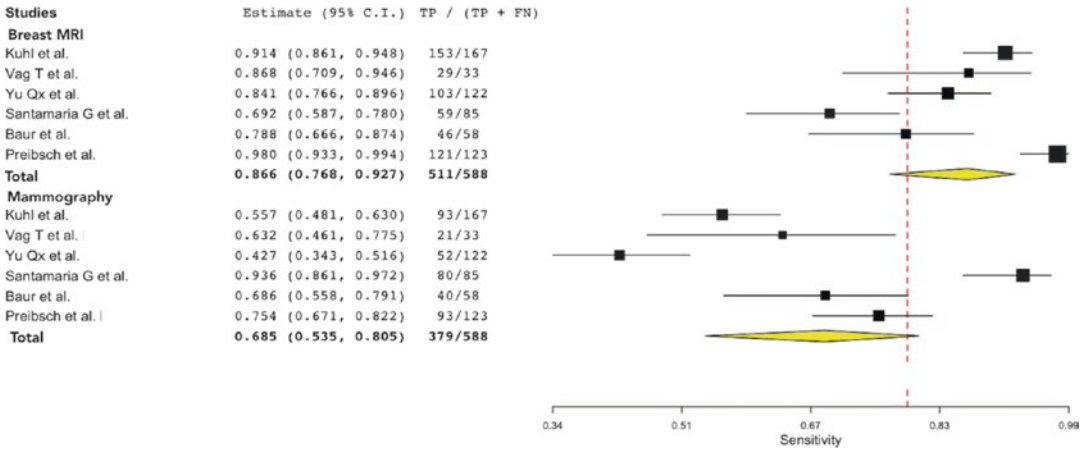

Fig. 8 Comparative sensitivity of mammography and contrast-enhanced MRI taken from a random sample of the available literature. The black rectangles correspond to single-study sensitivity estimates, while the black lines denote the 95% confidence intervals of these findings. The yellow diamonds represent pooled (random effects model) subgroup estimates with their 95% confidence intervals

positive tumors more often present as focal enhancement, while high-grade, estrogen receptor-negative tumors are usually larger in size and present with a clumped, segmental enhancement (Esserman et al. 2006). In addition, low-grade lesions more often lack enhancement on MRI (Facius et al. 2007; Kuhl et al. 2007; Vag et al. 2008), though this is not a robust predictor (see Fig. 7). Some authors investigated the use of diffusion-weighted imaging (DWI) and peak enhancement to distinguish low- from high-grade tumors. High-grade DCIS is characterized by lower apparent diffusion coefficient (DWI) value and higher peak initial enhancement (Iima et al. 2011; Rahbar et al. 2012). If FDG PET might also play a role in identifying DCIS with a worse prognosis by identifying an increased uptake of radioactive labeled glucose as suggested by preliminary evidence is yet unclear (Graña-López et al. 2019).

Mammography and ultrasound can play a role in diagnosing the presence of an invasive component after a histological diagnosis of DCIS. The presence of a mass, architectural distortion, or focal asymmetry should always raise the suspicion of an associated invasive component (Sim et al. 2015). In addition, the presence of a palpable mass and a large diameter and the presence of BI-RADS 5 characteristics at imaging can indicate the presence of an invasive component. In these cases, the use of a larger needle or the acquisition of more samples at biopsy might be indicated to ensure a correct diagnosis (Schulz et al. 2013; Hogue et al. 2014).

Elastography has also been proposed as a method to identify DCIS at higher risk of being associated with an invasive carcinoma. The size of the US finding and an increased stiffness have been associated with an increased risk of an associated invasive carcinoma, but the published results are rather heterogeneous (Evans et al. 2016; Bae et al. 2017; Shin et al. 2019). Currently, while US may suggest the presence of an invasive component, it is not possible to reliably distinguish DCIS from invasive breast cancer based on mammography and ultrasound (Londero et al. 2007; Scoggins et al. 2015; Shin et al. 2019).

In addition to a superior lesion extent mapping during preoperative evaluation, MRI can also suggest the presence of an invasive component associated with DCIS. The presence of a spiculated mass as opposed to non-mass enhancement only, the size of the lesion, and a presence of a heterogeneous enhancement in a non-mass lesion are all factors associated with a higher percentage of an associated invasive component (Hahn et al. 2013; Lee et al. 2016; Lamb et al. 2019). In addition, DWI may play a role in this setting: despite an inter-study variability in ADC values, the presence of an invasive breast cancer component is associated with significantly lower ADC values (Bickel et al. 2015).

5 Preoperative and Intraoperative Management of DCIS

Chemotherapy and hormonal therapy currently have no role in the preoperative management of DCIS (NICE 2018; Morrow et al. 2016; Ditsch et al. 2019), and after diagnosis and evaluation of the extension of disease (Kandel et al. 2020), surgery is performed.

In case with larger area of microcalcifications or enhancement, extending for more than one quadrant, mastectomy is generally indicated (Sakorafas and Farley 2003). Mastectomy should also be preferred in patients with multiple tumors and persistent positive margins after re-excision and in all the cases in which irradiation after surgery is contraindicated (Sakorafas and Farley 2003). For the cases in which breast-conserving surgery (BCS) with or without radiation therapy is feasible, a precise localization of the malignant area is mandatory prior to surgery.

Three methods are mostly used for the preoperative localization of DCIS (Chan et al. 2015):

- Wire-guided localization
- Radioactive seed localization (RSL)
- Radioguided occult lesion localization (ROLL)

Depending on the localization and the extension of the tumor, one or more wires can be placed, to ensure a complete resection of the tumor with sufficient free margins to reduce the risk of recurrence (Mannu et al. 2020).

Both wire localization and localization methods with radioactive tracers showed a high accuracy (Chan et al. 2015), and the choice of how to perform the preoperative localization is currently mostly guided by surgeons and radiologists' expertise and preferences (Niinikoski et al. 2019; Agahozo et al. 2020).

The intraoperative evaluation of the resection margins is advised in order to reduce the number of reoperations (Harness et al. 2014). The intraoperative histological evaluation of the surgical margins seems to be the most effective technique to evaluate margin status (Laws et al. 2016). In DCIS presenting with microcalcifications, the evaluation of the surgical specimen with mammography can help determining the complete excision of the malignant lesion. In the last years, the classical mammography of the surgical specimen has been progressively substituted with remote intraoperative specimen mammography, performed in the surgical block instead of the radiology unit, thus saving time and facilitating the procedure and communication between radiologists and surgeons (Mariscotti et al. 2020) (Fig. 9). In addition, digital breast tomosynthesis systems have been implemented for intraoperative specimen imaging, which improves the evaluation of soft tissues and the overall accuracy of the specimen evaluation (Garlaschi et al. 2019).

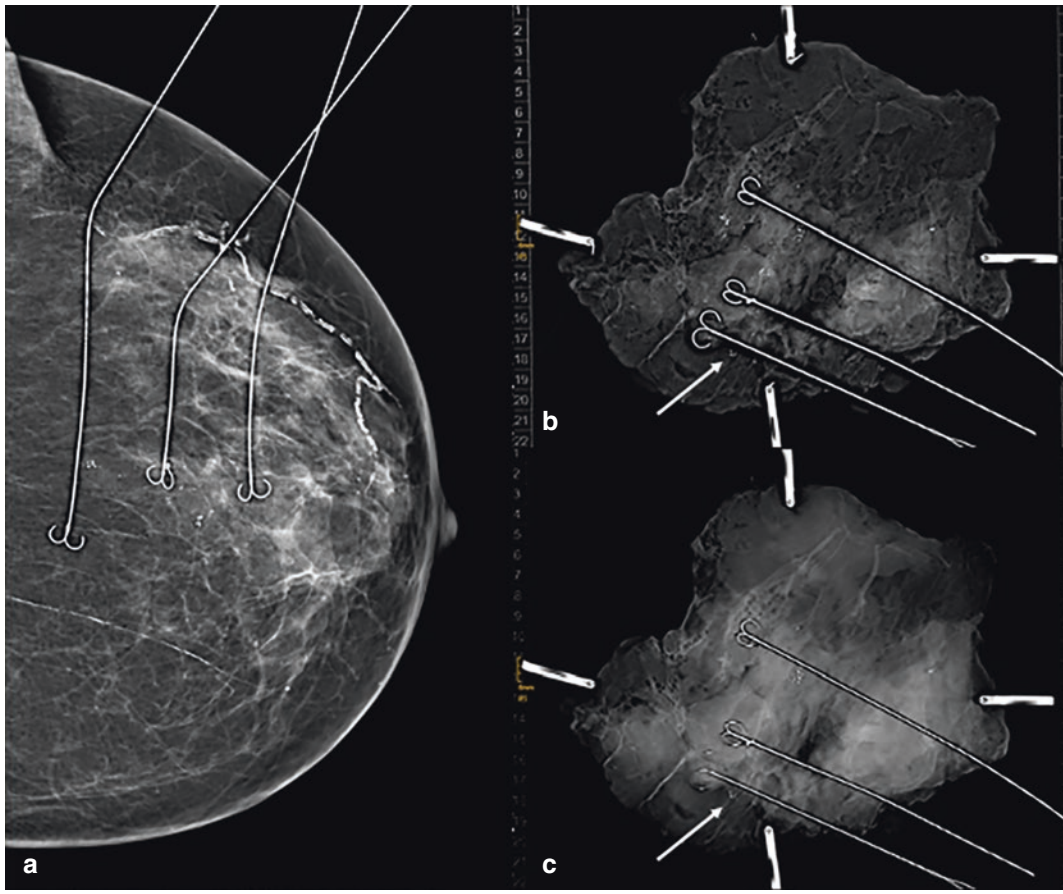

Fig. 9 Postmenopausal asymptomatic woman with a high-grade ductal carcinoma in situ. A preoperative stereotactic guided wire localization was performed. Three hook wires were used to precisely circumscribe the area with microcalcifications (**a**, craniocaudal control mammography). Mammography (**b**) and DBT (**c**) of the surgical specimen were performed, which showed close margins in the anterior margin of the specimen (arrow in **b** and **c**). This finding was confirmed at the histological evaluation

6 Conclusion

In conclusion, imaging plays a major role in the diagnosis of DCIS, a non-obligate precursor lesion to invasive DCIS. Currently, digital mammography remains the most important imaging method in diagnosing DCIS due to its implementation in national screening programs and its ability to detect microcalcifications as an imaging hallmark of DCIS. However, its lack of specificity causes problems: diagnosis of microcalcifications requiring unnecessary invasive and expensive biopsies that ultimately turn out as benign and diagnosis of biologically irrelevant disease that will never progress into invasive breast cancer. Further imaging tests have been investigated to resolve this issue with varying success: while the use of additional breast MRI can largely exclude breast cancer in general and specifically invasive breast cancer with very high NPVs and may thus obviate the need for biopsies of mammographic microcalcifications, the ability of different modalities to distinguish biologically aggressive from less aggressive DCIS is—though encouraging results have been published in particular for diagnosing invasive breast cancer associated with DCIS—less well explored.

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