Review Article

Contemporary management of ductal carcinoma in situ and lobular carcinoma in situ

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Abstract: The management of *in situ* lesions ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) continues to evolve. These diagnoses now comprise a large burden of mammographically diagnosed cancers, and with a global trend towards more population-based screening, the incidence of these lesions will continue to rise. Because outcomes following treatment for DCIS and LCIS are excellent, there is emerging controversy about what extent of treatment is optimal for both diseases. Here we review the current approaches to the diagnosis and treatment of both DCIS and LCIS. In addition, we will consider potential directions for future management of these lesions.

Keywords: Ductal carcinoma in situ (DCIS); lobular neoplasia (LN); lobular carcinoma in situ (LCIS)

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Introduction

Histopathologically, lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) are differentiated from invasive carcinoma by the confinement of malignant cells to the basement membrane (1). Historically, these two *in situ* carcinomas were considered obligate precursors to invasive lesions (1). However, recent genomic and transcriptomic analyses indicate molecular similarities in *in situ* and invasive cancers within the context of histologic grade as opposed to stage of progression (2,3). Specifically, comparisons of low grade DCIS and low grade invasive ductal cancer (IDC) to high grade DCIS and high grade IDC show genomic differences in ploidy level, karyotype and amplification (2). Estrogen receptor expression and activation among these lesions has been also been implicated in the progression to invasive disease (4). Moreover, the work of Hanahan *et al.* on the hallmarks of cancer have contributed to the evolution of our understanding of tumorigenesis and moved us towards consideration of both DCIS and LCIS as non-obligate precursors along the broad spectrum of malignant progression (5). Thus, the progression from DCIS and LCIS to invasive cancer is not assured, but rather a complex process involving interactions between genetics and the microenvironment at the molecular level (5,6).

Epidemiology

The implementation of population-based screening in North America and Europe has resulted in a marked increase in the incidence of *in situ* cancers (1,7). In developing countries, the practice of opportunistic breast screening has resulted in a dearth of information about the true incidence of *in situ* cancers (8), as in these settings, DCIS and LCIS are more likely to be diagnosed based on imaging and concomitant core needle biopsy (CNB) prompted by the presence of symptoms (9). As a result, it is difficult to determine the incidence and prevalence of these *in situ* lesions in countries in which breast cancer screening is not widely implemented.

In literature from the United States, the incidence of

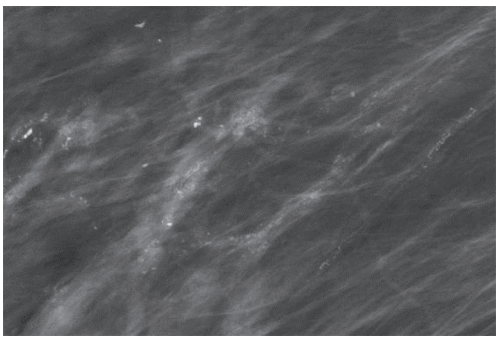

Figure 1 DCIS, high grade. Lesion presenting as new pleomorphic calcifications in a segmental distribution which represented intermediate grade cribriform/papillary DCIS on core biopsy. DCIS, ductal carcinoma in situ.

LCIS on open surgical biopsy is between 0.5% and 3.8% and ranges from 0.02% to 3.3% on core needle biopsies (10-12). Population screening data from South Australia detected LCIS in 5.3% of *in situ* specimens (13). Estimates from the Breast Cancer Surveillance Consortium (BCSC) in the United States reports that DCIS represents 24.9% of all cancers detected on screening (14). This figure corresponds with data from population-based screening programs in Turkey, Singapore and South Australia reporting 22%, 26% and 20% DCIS respectively (13,15,16). When compared to countries in Europe, such as Switzerland, the Netherlands and Italy, it appears that the US has the highest rates of DCIS (17). In China, where population-based screening is still not widely practiced, Si *et al.* in their 20-year review noted only 2.4% of the 4,968 sample population were diagnosed with DCIS/LCIS (18).

Risk factors

The risk factors for the development of *in situ* and invasive cancers are similar. These factors include family history and genetic predisposition, increased mammographic breast density and a history of atypia on breast biopsy (1). For women with a family history of breast cancer, Claus *et al.* calculated a 48% (OR 1.48) and 68% (OR 1.68) increased risk of DCIS and LCIS respectively compared to women with no family history of breast cancer. However, there was no association seen between alcohol consumption, smoking or oral contraceptive (OCP) use and risk of *in situ* carcinoma (19). A review of the data shows no consensus on the risk of developing *in situ* cancers and the use of hormone replacement therapy, although exogenous hormones are likely to contribute to incidence of DCIS as well as for invasive cancers (17,19).

Ductal carcinoma in situ (DCIS)

Imaging

The primary contributor to increased detection of DCIS is implementation of widespread screening mammography, starting in the United States in the 1980s. Whereas DCIS was rarely diagnosed before the use of mammography, it now accounts for an estimated 50,000 new breast cancers detected in women annually (20). DCIS most frequently presents as incidental microcalcifications on screening mammography. Only 10% of DCIS are associated with other imaging findings, including asymmetric density or mass (*Figure 1*) (21,22). BIRADS morphologic classification categorizes microcalcifications as amorphous, coarse heterogeneous, fine pleomorphic, fine linear, dystrophic or round, with the highest risk of DCIS seen with the fine pleomorphic and fine linear classifications (23,24). In some studies, digital mammography has been shown to have greater sensitivity for detection of DCIS than screen-film mammography, particularly among pre- and perimenopausal women (25,26). Interestingly, breast tomosynthesis, or "3-D mammography" while reducing call-backs, has not resulted in increased detection of DCIS (27).

The benefit of magnetic resonance imaging (MRI) in the routine management of DCIS has yet to be determined. MRI may have a possible role in preoperative workup in some women, especially in the setting of multifocal disease which can sometimes preclude breast conserving surgery (BCS). In this setting, MRI has been shown to have improved sensitivity over mammography in detecting multicentricity (28-30). In determining extent of disease, MRI can both underestimate DCIS compared to mammography (31) as well as overestimate DCIS. Therefore, MRI alone should not be used as an indication for mastectomy, although it may guide the need for further evaluation (32).

The potential advantages of MRI are reduced re-excision rates, identification of contralateral breast cancer at an earlier stage, and decreased local recurrence; however, these potential benefits have not been clearly established in published studies. Limited data have shown that preoperative MRI may have no significant impact on re-excision rate, margin status, or margin width (33-35).

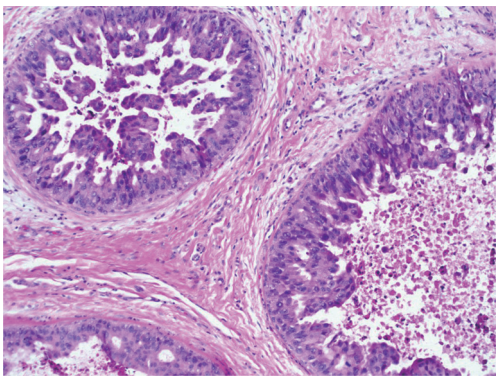

Figure 2 DCIS, high grade (100×). High nuclear pleomorphism, cellular cohesion and architectural complexity of high-grade DCIS are hallmarks of this neoplastic proliferation. DCIS, ductal carcinoma in situ.

Moreover, increased sensitivity of breast MRI comes at the cost of increased resource utilization, heightened patient anxiety, and a propensity for more patients to opt for mastectomy, regardless of the results of the MRI (7,33,36). In one study only preoperative MRI and age were independent predictors for receipt of mastectomy (33). MRI can be useful for screening the contralateral breast, resulting in identification of contralateral breast cancer in 2.6% of patients (36). This may be one factor contributing to higher contralateral mastectomy in women diagnosed with unilateral DCIS (37). However, the majority of contralateral mastectomies are still performed in women with unilateral DCIS, underscoring the possible unintended consequences of increased MRI evaluation.

Pathology

The World Health Organization (WHO) defines DCIS as a neoplastic intraductal lesion characterized by increased epithelial proliferation, presence of subtle to marked cellular atypia and an inherent but not necessarily obligate tendency for progression to invasive breast cancer (38). In pure DCIS, the intraductal epithelial cells are separated from the breast stroma by an intact layer of basement membrane and myoepithelial cells. DCIS is further separated into comedo and non-comedo types, based on the presence of necrosis (*Figure 2*). In 2009, the College of American Pathologists (CAP) and the American Society for Clinical Oncology (ASCO) established guidelines for pathology reporting of DCIS, requiring defining DCIS lesions as low, intermediate or high grade, with nuclear grade determined using six morphologic features: pleomorphism, size, chromatin, nucleoli, mitoses and orientation (39).

The pathologic assessment of DCIS can often be difficult, with even experienced breast pathologists often disagreeing on which characteristics constitute a diagnosis of DCIS (40,41). The morphologic distinction between atypia and low grade DCIS can often be subtle, requiring specialized expertise in some cases to render a diagnosis. Multicentricity can be encountered in DCIS; moreover, skip lesions can be seen leading to difficulty in margin assessment (42,43).

For DCIS diagnosed on core biopsy, occult invasion may sometimes be identified. Despite the use of larger gauge stereotactic devices, the incidence of upstaging at the time of surgical excision remains 20–25% (44-46). The possible identification of invasive cancer at the time of definitive excision should be discussed with patients, who must be advised that findings on final pathology may result in additional treatment recommendations.

Important challenges remain in the pathologic assessment of DCIS, particularly in reporting size and margin status. In addition, there are known disagreements between pathologists in how best to distinguish some DCIS from other epithelial lesions such as atypical ductal hyperplasias. However, substantial work has resulted in consensus for pathologic assessment for DCIS reporting criteria, including synoptic data elements that have facilitated both research and treatment.

Surgical management

Surgery for DCIS is aimed to prevent progression to invasive cancer with the attendant risks of disease dissemination and cancer mortality. NCCN guidelines for treatment of DCIS recommend excision of all disease to negative margins, with either BCS or mastectomy (47). Radiation is often recommended as part of BCS to reduce risk of local recurrence, based on randomized trial data. Treatment trends for DCIS over the past 20 years in the United States demonstrate a reduction in unilateral mastectomy with a resulting increase in lumpectomy and radiation (1,48). The most striking trend however, is the increase in bilateral mastectomy for unilateral DCIS, which is currently used to treat almost 10% of all newly diagnosed cases of DCIS. Important to note is that the choice of surgery or radiation have not been shown to impact disease specific mortality, indicating that surgical options should be considered in the context of patient values, risk aversion,

and competing comorbidities (48).

Mastectomy

Currently, almost a third of women diagnosed with DCIS in the United States will undergo mastectomy for their disease. Generally, mastectomy is indicated in patients with DCIS for extensive and/or multifocal DCIS involving more than one quadrant or in women with a contraindication for breast irradiation, such as prior irradiation or history of collagen vascular disease. However, patient preference remains the most important consideration in surgical treatment planning (49). In addition to simple mastectomy, skin-sparing mastectomy and nipple-sparing mastectomy are being used increasingly for DCIS. Overall, both skin-sparing and nipple sparing approaches have been shown to be oncologically safe with low recurrence rates (50-52). The good outcomes in these studies may be attributable to careful patient selection, involving exclusion of patients with centrally located disease, extensive DCIS, or radiographic abnormalities in close proximity to the nipple-areolar complex (53). Since the risk of distant metastasis with DCIS is negligible, the reason for performing mastectomy or BCS should be based on the extent of disease. The long-term risk of local recurrence following mastectomy is excellent at 1–2% in most series.

Lumpectomy

BCS is the most commonly employed surgical procedure in patients with DCIS. Since up to 90% of DCIS is nonpalpable and usually not visualized on ultrasound, various imaging-based localization techniques have been used to more precisely target the area of DCIS for excision. The most commonly used approach is that of wire localization, with either a single wire for focal calcifications or bracketed wires for more extensive regions of involvement. Recently, radioactive seed localization has been used in some institutions to allow for more focal targeting of nonpalpable lesions, with excellent results reported (54). Regardless of the localization technique used, confirmation of retrieval of the targeted lesion on a specimen radiograph is an essential and required component of the procedure.

BCS is more challenging for DCIS than for invasive cancer, due to the greater difficulty in obtaining negative margins secondary to the more discohesive growth pattern. In one study, only DCIS and whether additional shave margins were obtained were predictive of a positive lumpectomy margin (55). Although the optimal size of a negative margin for DCIS remains a matter of debate, it is clear that recurrence is highly associated with a positive margin, and most surgeons aim to achieve at least 1–2 mm margins for DCIS, even at the cost of multiple re-excisions.

Surgical management of the axilla

The American Society of Clinical Oncology (ASCO) clinical practice guideline update for sentinel lymph node biopsy (SLNB) in early stage breast cancer supports the use of SLNB for DCIS in women undergoing mastectomy. This recommendation is in part due to the known incidence of upstaging from core biopsy to surgical excision (56), as well as concerns regarding the potential for technical challenges in performing SLNB following disruption of lymphatics between the breast and axilla. In unselected DCIS, the rate of positive sentinel node involvement ranges between 5–10%, many of which consist of isolated tumor cells or micrometastases (57-61) (*Table 1*). Data support that the outcomes for those DCIS patients with small volume nodal disease do not differ from those with negative nodes, further advocating against routine SLNB for DCIS.

Radiation

In the United States, adjuvant radiation therapy (RT) following wide local excision for DCIS remains standard of care, although the NCCN guidelines include the option of excision only for low risk DCIS. There have now been five prospective randomized trials comparing lumpectomy alone to lumpectomy with radiation in women with DCIS (*Table 2*) (62-66). Overall, ipsilateral breast recurrences can be reduced by more than half with adjuvant radiation, with the absolute magnitude of benefit dependent on baseline recurrence risk. The benefit of radiation was seen in all subgroups regardless of age at diagnosis, extent of breast-conserving surgery, use of tamoxifen, method of DCIS detection, margin status, focality, grade, comedonecrosis, architecture, or tumor size. Based on these studies, most women with DCIS are recommended to consider adjuvant RT to reduce the risk of local recurrence.

Despite a clear proportional benefit of RT in all subsets of patients undergoing lumpectomy for DCIS, wide excision alone has gained increasing attention as an alternative to lumpectomy with RT among some subgroups of women with low-risk DCIS who are at sufficiently low

Table 1 Summary of randomized trials for DCIS comparing lumpectomy alone to lumpectomy plus adjuvant radiation

Author/country	n	Follow up, months	Ipsilateral DCIS or invasive recurrence rate, LR group	Ipsilateral DCIS or invasive recurrence rate, L group	Outcomes (relative risk reduction with LR *vs.* L*, 95% CI)		
					Ipsilateral DCIS or invasive recurrence	Ipsilateral invasive recurrence	Contralateral DCIS or invasive cancer
McCormick, 2015, USA, LR *vs.* L	636	86 (median)	0.9%	6.7%	0.10 (0.02, 0.41)	–	1.07 (0.48, 2.39)
Holmberg, 2008, Sweden, LR *vs.* L	1,046	101 (mean)	12.2%	27.1%	0.45 (0.34, 0.59)	0.59 (0.40, 0.86)	1.25** (0.73, 2.13)
Bijker, 2006, Europe, LR *vs.* L	1,010	126 (median)	14.8%	26.2%	0.56 (0.44, 0.73)	0.60 (0.41, 0.87)	1.38 (0.86, 2.21)
Houghton, 2003, UK, Australia, New Zealand, LR or LR-Tam *vs.* L or L-Tam	1,694	52.6 (median)	4.8%	13.2%	0.38 (0.25, 0.59)	0.45 (0.24, 0.85)	0.82 (0.34, 1.18)
Fisher, 1998, USA, LR *vs.* L	818	43 (mean)	13.3%	31.0%	0.43 (0.31, 0.59)	0.41 (0.23, 0.71)	1.60 (0.74, 3.43)

*, LR, lumpectomy and radiation; L lumpectomy only. **, invasive cancer only. DCIS, ductal carcinoma in situ.

Table 2 Studies reporting outcomes of SLNB for DCIS with distribution of nodal burden

Author/institution	n	Total SLNB (+) for metastasis	Nodal burden			Comments
			Isolated tumor cells (ITCs)	Micro-metastases	Macro-metastases	
Francis, 2015, MD Anderson	1,234	10.7%	5.4%	2.9%	2.4%	Patients who had pure DCIS with and without positive SLNs had equivalent survival rates (100.0% *vs.* 99.7%; P=NS) at 61.7 months
Tunon-de-Lara, 2015, France, multicenter	192	13.5%	3.6%	4.2%	5.7%	Mastectomy only
Dominguez, 2008, Harvard Hospitals	179	11.3%	10.2%	1.1%	0%	Mastectomy only
Moore, 2007, USA, multicenter	470	9.0%	7.6%	0.8%	0.6%	"High risk" DCIS; 1 patient with ITC in cohort developed liver metastasis at 27 months median follow up
Fraile, 2006, Spain, multicenter	142	7.0%	0%	5.6%	1.4%	"High risk" DCIS; conversion rate to invasive cancer 39%. (+) SLN in 1% of DCIS and 19.5% of DCIS upstaged to IDC

SLNB, sentinel lymph node biopsy; DCIS, ductal carcinoma in situ; ITC, isolated tumor cell; IDC, invasive ductal cancer.

risk of recurrence that they may not derive meaningful clinical benefit from radiation. The most recently completed study was conducted by the Radiation Therapy Oncology Group (RTOG), which reported results from a prospective randomized trial that allocated low risk DCIS to radiotherapy or observation following lumpectomy for DCIS (62,67). Even in this low risk cohort, defined as low-intermediate grade DCIS smaller than 2.5 cm with at least 3 mm margins, local failure at 7 years was significantly improved when lumpectomy was followed by radiotherapy

(0.9% *vs.* 6.7%, P≤0.01). However, it has been argued that this difference may be too small to be clinically meaningful and these data may in fact support lumpectomy alone in this favorable group.

Several single-arm studies of excision without radiation have also been reported. The largest of these was the Eastern Cooperative Oncology Group (ECOG) 5194 trial, a multi-center trial of lumpectomy alone in women with DCIS at low risk for recurrence, based on clinical and pathologic criteria (68,69). Eligible patients were required to have low- or intermediate-grade DCIS, tumor size of ≤25 mm (cohort 1), or high-grade DCIS, tumor size of ≤1.0 cm (cohort 2), and a minimum negative margin width of ≥3 mm or no tumor on re-excision. At a median follow-up of 12.3 years, the 12-year rates of developing an ipsilateral breast event (IBE) were 14.4% for cohort 1 and 24.6% for cohort 2 (P=0.003). Twelve-year rates of developing an invasive IBE were 7.5% and 13.4%, respectively (P=0.08). A smaller single arm study of 158 patients treated for DCIS with wide excision alone at the Harvard hospitals was recently updated (70). At a median follow up of 11 years, 19 patients (13%) had LR as a first event of which 13 were DCIS only and six were invasive. The 10-year estimated cumulative incidence of LR was 15.6%.

There has been recent interest in the use of accelerated partial breast irradiation (APBI) for DCIS. According to the ASTRO consensus statement, DCIS less than 3 cm can be treated with APBI with caution (71). To date, the largest cohort of women with DCIS treated with APBI demonstrated an ipsilateral breast tumor recurrence of 2.6% at 5 years with no regional recurrences (72). Other smaller studies (73-75) suggest that APBI in DCIS is equivalent to APBI in early breast cancer. At present, there is consensus that DCIS can be treated with caution using ABPI techniques; however longer follow-up will determine whether this benefit is durable.

Endocrine therapy

The use of adjuvant endocrine therapy for DCIS is aimed to reduce both ipsilateral breast recurrences in women undergoing lumpectomy as well as new contralateral breast events. However, the tradeoff between clinical benefit and side effects has not provided a clear advantage in favor of endocrine therapy for all patients, particularly in those with low risk disease or hormone receptor-negative DCIS. Two prospective randomized trials have provided some insight in how tamoxifen might be best applied: in NSABP B24 women treated for DCIS with BCS and radiation were randomized to either tamoxifen or placebo. Overall, women treated with tamoxifen had a 30% reduction in breast cancer-free survival, with the benefit restricted to ER(+) DCIS (76). In the UK, Australia, New Zealand study, patients with DCIS treated with lumpectomy were randomized to in a 2×2 design to either tamoxifen, radiation, both, or neither. At a median follow up of 12.7 years, women randomized to tamoxifen had a significant 29% reduction in both ipsilateral and contralateral events, but the benefit was limited to those women who did not have radiation (77). Aromatase inhibitors (AIs) are also emerging as potentially beneficial in this setting. NSABP B-35 randomized women after lumpectomy to either tamoxifen with radiation or anastrozole with radiation and found that anastrozole was superior to tamoxifen event-free survival in women younger than 60 years of age (78). Taken together, these studies suggest that endocrine therapy may play a role in patients with hormone receptor-positive disease who decline radiotherapy, and that future studies will help refine indications for AI in the management of DCIS.

Active surveillance

There has been interest in recent years in active surveillance for low risk DCIS, in part based upon the recognition of the tremendous biological heterogeneity in the group of conditions defined as "DCIS". Although there is ongoing work on identifying those biomarkers which could help identify the lowest risk DCIS with sufficiently low risk to warrant surveillance rather than excision, no specific marker has emerged to provide sufficiently accurate risk stratification. The first such clinical trial randomizing patients with low risk DCIS (age >45, grade 1 or 2 DCIS) to active surveillance with or without endocrine therapy was activated in the UK in 2014. Named the "LORIS" study, the trial is aimed to determine how invasive cancer incidence, overall and breast cancer specific survival are impacted with surveillance alone (79). In the United States, the COMET study will aim to address this question in a cohort of low risk, ER-positive HER2-negative DCIS.

Lobular carcinoma in situ (LCIS)

Detection and diagnosis

Since first proposed by Haagensen *et al.* in 1978, and

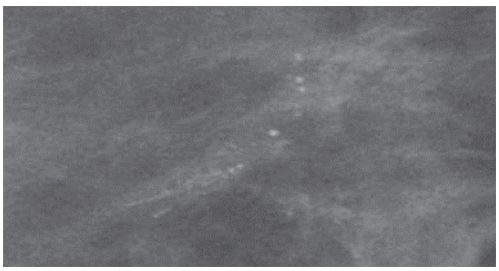

Figure 3 Classic LCIS. Linear calcifications in a grouped distribution prompted recommendation for biopsy which showed classic LCIS. This mammographic finding is indistinguishable from those commonly observed with DCIS. LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ.

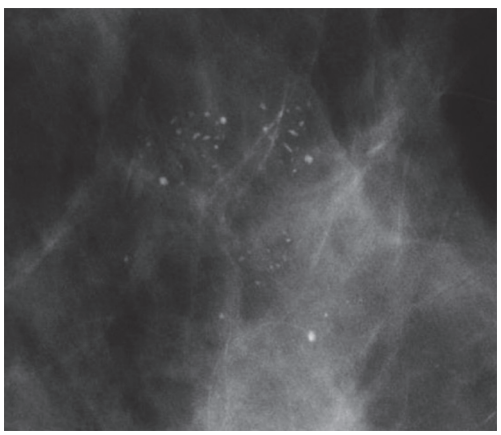

Figure 4 Pleomorphic LCIS. Pleomorphic calcifications in a grouped distribution representing intermediate grade pleomorphic LCIS. LCIS, lobular carcinoma in situ.

subsequently used in the WHO classification of breast tumors, the term lobular neoplasia (LN) has been used to encompass the histopathologic spectrum of atypical lobular hyperplasia (ALH) and LCIS (6,9). LCIS is further subdivided into classic lobular carcinoma in situ (CLCIS) and pleomorphic lobular carcinoma in situ (PLCIS) (80). Due to a lack of distinctive physical exam findings, or pathognomonic findings on imaging, ALH, CLCIS and PLCIS are usually found incidentally in biopsy specimens (81). Characteristically, LN has a propensity to be bilateral and multifocal (82).

Although the terminology of LN has been in the literature for many years it is not uniformly used (81). Specifically, some authors use LN without differentiating between the subtypes (ALH, LCIS, PLCIS) in their analysis while others make distinctions between the subtypes of LN. The importance of distinguishing between the subtypes of LN lies in the differences in risk of breast cancer. LCIS confers a much higher risk (9–10 times increased risk) of breast cancer than ALH (4–5 times increased risk) (83). Moreover, further distinction of LCIS as CLCIS or PLCIS is important due to the difference in recommendations for management (84).

In addition to being a risk factor, LN has also been shown to be a non-obligate precursor based on comparable histologic and molecular profiles to invasive lobular cancer (ILC) (85-87) and a higher risk of ipsilateral breast cancer compared to the contralateral breast (9). Furthermore, in contrast to women of average risk, individuals with LN have an increased probability of developing ILC (18-fold increase) as opposed to IDC (3- to 4-fold increase) (9,81,88).

Mammography is the most sensitive imaging modality for LN (9). Due to a transition from film screen mammography (FSM) to digital screen mammography (DSM) there has been a threefold increase in the detection of high risk lesions such as LN (89). Punctate microcalcifications are the most common radiologic finding of LCIS on mammography (90). However, it should be noted that there is a difference in the prevalence of mammographic findings between PLCIS and CLCIS. Specifically, PLCIS is more likely to present with microcalcifications, architectural distortion and/or density (*Figures 3*,*4*) (82).

On MRI, LN typically appears as an area of non-mass-like enhancement (91). The use of MRI as a screening modality for patients with LCIS is somewhat controversial in light of differing recommendations from the American Cancer Society (ACS) and the NCCN (92). Current recommendations from the ACS states there is insufficient evidence to support or oppose the use of yearly MRI screening among patients with LCIS (93). Alternatively, the NCCN recommends consideration of annual MRI for patients with a diagnosis of LCIS after the age of 30 (94). Studies have estimated an incidental cancer detection rate of 4% in patients with LCIS undergoing MRI (92,95). These findings correspond to cancer detection rates for patients with genetic abnormalities (e.g., BRCA mutations) screened with MRI; thus leading some authors to argue for MRI screening of patients with LCIS (96). However, MRI as an adjunct to conventional screening has not been proven to increase detection of early stage breast cancer or result in higher cancer detection rates when compared to conventional screening alone among individuals with LCIS (97). Additionally, use of screening MRI results in a

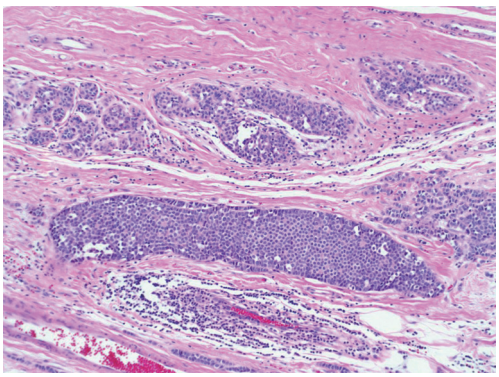

Figure 5 Classic LCIS (100×). Terminal duct lobular units are distended by a loosely cohesive, monomorphic population of small to medium-sized cells, resembling a "bag of marbles". LCIS, lobular carcinoma in situ.

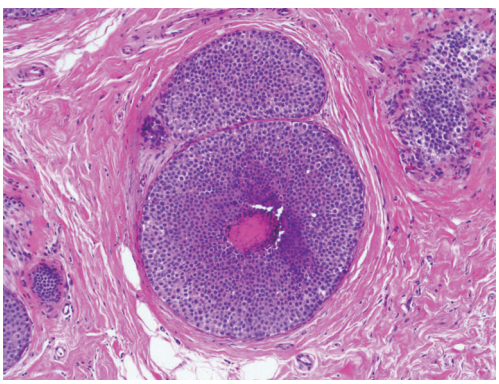

Figure 6 Pleomorphic LCIS (100×). Large, dyscohesive cells with abundant granular eosinophilic cytoplasm and moderate to marked nuclear pleomorphism characterize pleomorphic LCIS. The absence of the intercellular adhesion molecule E-cadherin in LCIS helps differentiate this lesion from high grade DCIS. LCIS, lobular carcinoma in situ; DCIS, ductal carcinoma in situ.

higher number of biopsies and more frequent follow up visits and evaluations (95). These inconsistencies in the literature underscore the persistent controversy around screening MRI in the LCIS population.

Despite these descriptions of image findings associated with LN it should be noted that the majority of LN, principally CLCIS, is not associated with any particular specific radiologic findings (9). The definitive diagnostic modalities for LN are CNB or open surgical biopsy. However, with a move away from surgical biopsy as the initial tissue acquisition modality image guided CNB is recommended as the first biopsy method used for diagnosis (98).

Pathology

The difference between ALH and LCIS, which has been described as "quantitative rather than qualitative", is dependent on the number of involved acini of a lobular unit (81). Specifically, CLCIS is defined as distension of more than half the acini of a lobular unit by a uniform and discohesive population of small atypical epithelial cells (80) (*Figure 5*). CLCIS is hormonally sensitive (estrogen and progesterone receptor positive) and generally does not overexpress Ki67 and human epidermal growth factor (Her-2) (82,99). The United Kingdom National Health Service Breast Screening Program (NHSBSP) has provided guidelines for this nomenclature, and currently recommends using the all-encompassing term LN instead of differentiating the subtypes as ALH or CLCIS, arguing that the distinction between CLCIS and ALH are arbitrary and subjective (6,100).

PLCIS is characterized by enlarged discohesive epithelial cells, irregular shaped nuclei and abundant eosinophilic cytoplasm (101) (*Figure 6*). Additional features such as comedo necrosis and calcifications found in PLCIS make it histopathologically similar to DCIS. Such similarities to DCIS have resulted in some authors arguing that PLCIS has an increased probability of progression to invasive cancer (82,84,102). In their retrospective review on the genetic and phenotypic characteristics of PLCIS, Chen *et al.* reported PLCIS was not hormonally sensitive (estrogen and progesterone receptor negative), exhibited a higher proliferation rate and overexpression of epidermal growth factor Her-2 (82). These finding further confirmed the similarities between PLCIS and DCIS. Immunohistochemistry staining shows both PLCIS and CLCIS lack staining for E-cadherin. Conversely, DCIS stains positive for E-cadherin enabling differentiation of PLCIS from DCIS with immunohistochemistry (9,82).

Treatment and management

The 2016 National Comprehensive Cancer Network (NCCN) guidelines for the management of LCIS recommend surgical excision for LCIS diagnosed on CNB (103). However, some have recently argued that this recommendation be revised based on new data. Multiple

studies, including one prospective study, have recently reported low upgrade rates ranging from 1–5% upon exclusion of specimens with high risk characteristics such as non-classic morphology, discordant imaging and pathology, and extensive LCIS (>4 foci) (90,104-106). Moreover, Ciocca *et al.* showed that the presence of LCIS at the margin of breast conservation therapy specimens (BCT) did not affect local recurrence (107). These low upgrade rates indicate that surgical excision provides little benefit for patients who present with concordant imaging and pathology with pure LN on CNB.

Active surveillance

As indicated above, LCIS is considered both a high-risk lesion and a non-obligate precursor which confers a 10–20% risk for development of breast cancer (9,103). Due to this designation, women with LCIS are classified as high risk and have different screening recommendations compared to average risk women. In particular, the NCCN guidelines recommend clinical breast exam (CBE) every 6–12 months in conjunction with an annual mammogram (103). In King *et al.*'s 29-year single institutional review of their experience with LCIS, surveillance was reported as the most frequently selected management modality. In this study, women who underwent surveillance without chemoprevention had a cancer rate (invasive ductal, invasive lobular or DCIS) of 7% and 21% at 5 and 10 years respectively. This was significantly higher than the 5-year 3% and 10-year 12% cancer (invasive ductal, invasive lobular or DCIS) rates reported for women in the cohort undergoing surveillance combined with chemoprevention (108).

Surgery

Historically, surgery has been at the cornerstone for the management of LN. At this time, recommendations from many of the major cancer organizations endorse excision of LN associated with any invasive cancer, DCIS or discordant radiologic and pathologic findings (6,81,103). However, the surgical management of pure LN has proved controversial. Based on Foote and Stewart's initial description of LCIS as a precursor to invasive lobular carcinoma (ILC), mastectomy was recommended to prevent the progression to ILC (81). Nonetheless, with new genetic and molecular information, in conjunction with better insight into the natural history of LN, the recommendation of surgery to prevent progression is no longer the prevailing paradigm (6).

Current surgical recommendations differ between PLCIS and CLCIS. Due to differences in the histological and molecular features between the subtypes surgical recommendations are different depending on the subtype. As mentioned previously, imaging-concordant pure CLCIS has a low risk of a concomitant invasive lesion; therefore, surgical excision is not warranted and it can be effectively managed with surveillance and chemoprevention (6,84,90). Due to concerns that PLCIS is more aggressive and exhibits histologic and molecular characteristics similar to DCIS, the NCCN, European Society of Medical Oncology (ESMO) and NHSBSP all recommend excision with negative margins (102). Flannagan *et al.* in their retrospective analysis on patients with PLCIS noted a high rate of upgrades to invasive cancer or DCIS (84). Pieri *et al.* in their systematic review reported a high rate of concomitant invasive disease with PLCIS and as a result, recommended surgical excision similarly to how DICS would be treated. However, they mentioned there is currently no evidence on the effectiveness of adjuvant therapy, such as radiation (102).

For patients with LN and other risk factors such as family history of breast cancer, genetic abnormalities, or extremely dense breasts bilateral prophylactic mastectomy (BPM) can be offered as a risk reduction strategy (6). Studies report a 90–95% risk reduction among patients who undergo BPM (109,110). However, there is general consensus that this represents a more invasive treatment than is warranted for most patients, particularly for those patients who lack genetic predisposition for breast cancer.

Chemoprevention

The American Society of Clinical Oncology (ASCO) and the NCCN recommend placing high-risk (Gail model risk ≥1.7% or history of LCIS) premenopausal women on selective estrogen receptor modulators (SERM) and post-menopausal women on AIs. Specifically, tamoxifen for premenopausal women and raloxifene or exemestane for post-menopausal women (6,103).

Multiple studies have established the risk reduction to invasive cancer conferred by chemoprevention in high risk populations. The National Surgical Adjuvant Breast and Bowel Project (NASBP) P-1 study was one of the early transformative studies in the management of patients with high risk lesions such as LCIS. Inclusion criteria for the study was age ≥60 years; age 35–59 years with at least a 1.66% 5-year predicted risk of breast cancer; or any age with

a history of LCIS. Participants were randomized to receive a placebo or 20 mg/day of tamoxifen. Results showed a 44%, 51%, and 55% risk reduction in women ≤49 years, between 50–59 and ≥60 years respectively. Moreover, there was a 56% risk reduction among women with a history of LCIS (111). These results were confirmed in the NSABP (STAR, P-2) trial which reported tamoxifen and raloxifene were equivalent in reducing the risk of invasive cancer. In addition, they noted raloxifene had a reduced risk of thromboembolic events and cataracts compared to tamoxifen (112). In the MAP.3 trial, exemestane use resulted in a 65% risk reduction in invasive cancer (113). These studies show chemoprevention as an acceptable alternative to surgery or active surveillance in appropriately selected individuals with LCIS.

Conclusions

The increased detection of *in situ* lesions on screening mammography has made both DCIS and LCIS important clinical entities. Currently, DCIS is treated as a precursor to invasive cancer, and LCIS as a risk factor for invasive cancer. However, evidence supports that both confer risk of invasive progression, including increased breast cancer risk to the contralateral breast. Emerging studies in the biology of DCIS and LCIS have revealed tremendous heterogeneity among *in situ* lesions. Such discoveries have the potential to provide better risk stratification of *in situ* disease, and will provide future opportunities to individualize treatment recommendations based upon extent of future cancer risk.

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Footnote

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