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Ductal Carcinoma In Situ and Progression to Invasive Cancer: A Review of the Evidence

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Abstract

Ductal carcinoma in situ (DCIS), breast cancer confined to the milk ducts, is a heterogeneous entity. The question of how and when a case of DCIS will extend beyond the ducts to become invasive breast cancer has implications for both patient prognosis and optimal treatment approaches. The natural history of DCIS has been explored through a variety of methods, from mouse models to biopsy specimen reviews to population-based screening data to modeling studies. This article will review the available evidence regarding progression pathways and will also summarize current trials designed to assess DCIS progression.

Key words: ductal carcinoma in situ; screening; invasive breast cancer; mammography.

Introduction

Ductal carcinoma in situ (DCIS), breast cancer confined to the milk ducts, is a heterogeneous entity clinically, histologically, genomically, and radiologically. The incidence of DCIS has increased over time, now comprising approximately 20% of screen-detected breast cancer cases; approximately 48 100 cases of screening and symptomatically detected DCIS occur yearly in the United States versus 268 660 invasive cases (1). Despite the relative frequency of DCIS on screening mammography, questions remain regarding its natural history. Because it is not possible to directly observe in vivo disease progression at the cellular level, there is uncertainty regarding the pathways leading an in situ process to become invasive as well as the percentage of cases of untreated DCIS that will lead to invasive disease (ID) over a period of time. This, in turn, has led some to question the impact of DCIS detection on mortality. The purpose of this article is to explore what is known about the natural history of DCIS and to examine current knowledge regarding pathways to ID. In addition, we will review the state of the field and summarize ongoing efforts to increase understanding of DCIS progression and clinical impact.

Definitions and Classifications

Ductal carcinoma in situ was first described in 1932 by Albert C. Broders as "a condition in which malignant epithelial cells and their progeny. . . have not migrated beyond the juncture of the epithelium and connective tissue or the so-called basement membrane" (2). Early definitions of DCIS were not always consistent, sometimes including disease with an invasive component (3). The current understanding of DCIS as an entity arising from the terminal duct lobular unit epithelial cells layering the basement membrane and without evidence of stromal invasion emerged more universally in the 1980s. Ductal carcinoma in situ is not uncommonly identified at autopsy (9% of cases in a meta-analysis) (4), although, as has been pointed out, many autopsy studies from earlier decades were performed on suboptimally preserved tissue and employed varying diagnostic criteria, impeding the understanding of prevalence (5).

There are several systems for classifying DCIS. Older systems relied on architectural features (comedo, cribiform, micropapillary, solid, and mixed subtypes) and had relatively poor reproducibility with high categorical overlap (6). Newer systems rely on nuclear grade and sometimes

Key Messages

- The incidence of ductal carcinoma in situ (DCIS) has increased over time, now comprising approximately 20%–25% of screen-detected breast cancer cases in the United States.
- Despite the relative frequency of DCIS on screening mammography, many questions remain regarding its natural history given the lack of ability to directly observe in vivo progression.
- Evidence for in situ to invasive progression is drawn from a variety of studies, including animal investigations, biopsy specimen review, population-based screening data, modeling studies, and, more recently, in-progress and planned DCIS surveillance trials.

features of luminal necrosis (6). This approach, resulting in division into high-, intermediate-, and low-grade DCIS, has better reproducibility (6,7). It must be noted, however, that categorization of low-grade DCIS is still less frequently agreed upon among pathologists (8), due to both underinterpretation (difficulty in distinguishing low-grade DCIS from atypical ductal hyperplasia) and overinterpretation (identifying low-grade disease as high-grade). Both have implications for assessing progression and determining optimal treatment.

Models of Progression

Ductal carcinoma in situ is considered to be a precursor to invasive carcinoma, but the invasive malignant potential of any individual case of DCIS varies, harking back to its heterogeneity. Several different models have been proposed to explain what might precipitate invasion at the cellular level (9). The independent evolution model assumes that distinct initiator cells give rise to either in situ or invasive subpopulations, less convincing because synchronous DCIS and ID usually demonstrate concordance in mutations and copy number aberrations (9). In contrast, direct evolution models propose that a single normal progenitor cell ultimately gives rise to in situ and invasive cells (9). The direct evolutionary bottleneck model envisions multiple somatic mutations arising within individual subclones, only one of which achieves invasion (9). The direct multiclonal model argues for the penetration of multiple clones after basement membrane integrity loss, although there is also debate about whether the cells themselves acquire the ability to penetrate the membrane or whether changes in the cellular stromal environment allow invasion to occur (9–11) (Figure 1).

Grade and Progression

Ductal carcinoma in situ often has similar genetic characteristics to coexisting synchronous or later metachronous

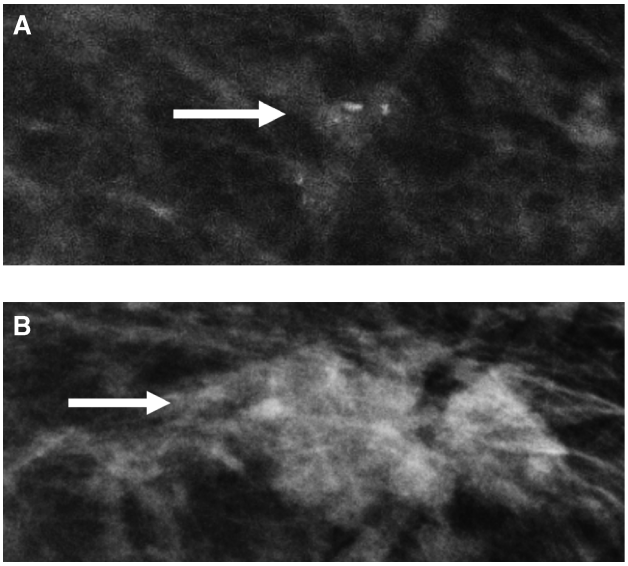

Figure 1. 55-year-old woman with grouped coarse heterogeneous calcifications in her left breast on screening mammogram, left craniocaudal view (**A**) (arrow). The calcifications were not investigated. The patient presented for screening three years later as per standard of care in the United Kingdom, where the mammogram (**B**) was performed. An irregular mass with spiculated margins (arrow) is now seen at the site of the calcifications, which are no longer visualized. US-guided core-needle biopsy was performed of a sonographic correlate (not shown), yielding grade 2 invasive ductal carcinoma (ER+, PR+, HER2-). It is not possible to know if the unbiopsied calcifications represented ductal carcinoma in situ, but this is a plausible scenario.

ID. There is robust evidence that high-grade in situ to invasive pathways are distinct from low-grade trajectories, also supporting a direct precursory link from DCIS to later ID (12,13) (Figure 2). Of interest, in contrast, recent work on atypical ductal hyperplasia suggests that atypical ductal hyperplasia may have multipotent trajectories, ultimately progressing to either low-grade or high-grade invasive disease (14). A distinct pathway is also suggested by imaging-based observations, demonstrated in a 2017 study from Germany evaluating 1970 cases of DCIS detected at prevalent round screening and subsequent first and second screening exams (15). Age-adjusted logistic regression was performed to assess grade-specific detection rates between the baseline screening round and later rounds. Overall detection rates were lowest for low-grade DCIS (0.11–0.25 per 1000 women screened) and highest for high-grade DCIS (0.53–0.59 per 1000). Low-grade detection was significantly lower at later screens compared to the prevalence round (OR = 0.79, $P = 0.006$; OR = 0.76, $P = 0.003$), but high-grade detection rates were maintained at the same higher levels at later rounds (OR = 0.89, $P = 1.43$; OR = 0.97. $P = 0.700$). This steady detection level of high-grade DCIS in conjunction with a maintained higher incidence rate compared to low-grade DCIS suggests that high nuclear grade DCIS has a relatively more rapid progression to ID (15).

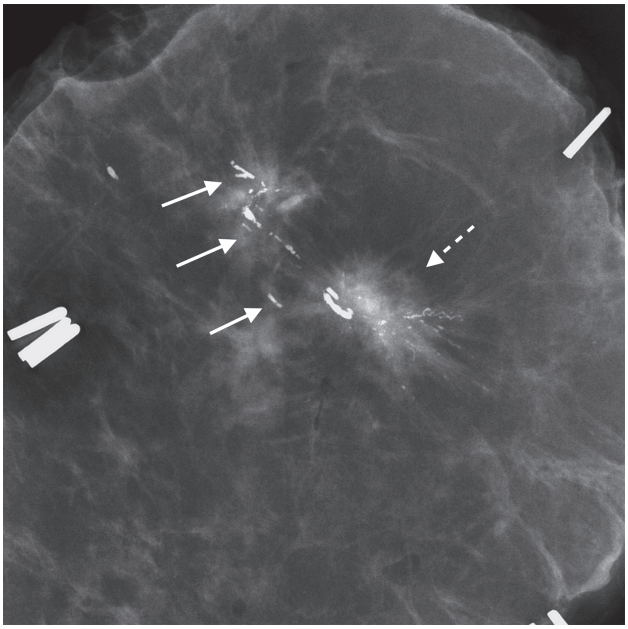

Figure 2. Specimen radiograph from a 70-year-old woman status post excision of a screening-detected mass with spiculated margins (dashed arrow) and associated fine linear and branching calcifications (solid arrows). Surgical pathology demonstrated grade 3 invasive ductal carcinoma with associated high nuclear grade ductal carcinoma in situ.

Evidence for Progression

What evidence exists for DCIS progression, and how has the relationship between DCIS and ID been investigated? Classifying the types of evidence currently available may aid our understanding of the state of current knowledge.

Animal Models

The development of animal (usually mouse) models has contributed to the understanding of the relationship between atypia, in situ disease, and ID, although the applicability of these models to human disease pathways is still uncertain. A 1999 consensus panel formally termed mouse hyperplasias with atypia that could progress to ID as "mammary intraepithelial neoplasia" and recommended that any such models include a distinct population of cells with atypical cytology or demonstrated association with a known cancer. The panel also recommended that mammary intraepithelial neoplasia be categorized into low- or high-grade based on epithelial layer number (16). Endogenous, chemically induced, and genetic mouse models have all been developed, fitting these criteria. In addition, xenograft models have been developed, involving transplantation of human breast hyperplasia into mouse mammary fat pads and, in some cases, into primary mammary ducts (17). Analyzing individual animal models is beyond the scope of this review, but the key takeaway is that in many of the mouse models, nearly 100% of mammary intraepithelial neoplasia will progress to ID, whereas only a few models—those using $p53^{-/-}$ outgrowth lines, for example—appear to follow a nonobligate pathway that may be most useful for increasing the understanding of human DCIS to ID pathways (18). A recent review argues that further work needs to be done to develop animal models fully representing human disease, suggesting that a combined xenograft model with genetically engineered models and humanized stromal tissue may be most optimal (16).

Biopsy Specimen Review (Untreated DCIS Studies)

Several studies have retrospectively assessed purportedly "benign" breast biopsy specimens to identify cases of DCIS originally misinterpreted as nonmalignant. The patients, who therefore did not undergo treatment or who underwent delayed treatment only, are then followed to determine clinical outcome and to identify any development of ID. Such studies are intrinsically imperfect because the biopsy itself may theoretically affect the course of the disease. In addition, there is a potential selection bias favoring low-grade disease, less likely to be identified initially; this may in turn lead toward underestimation of progression. As well, existing studies, with biopsies performed in a prescreening era, are usually composed of a small case numbers and often rely on older architectural classifications for DCIS, meaning that outcomes are harder to evaluate due to outdated histopathologic categorization (19). However, these studies offer at least some insight into DCIS progression.

In an oft-cited review, Erbas and colleagues assessed this initially misclassified "benign" biopsy data, finding that between 14% and 53% of DCIS cases progressed to ID over a period of 10 or more years (20). However, even the larger studies entailed only a relatively small number of cases, a limitation of the data (19,21,22). Betsill and colleagues, for example, reviewed breast biopsies performed between 1940 and 1950, and only 25 women were found to have undiagnosed low-grade DCIS (referred to as "low-grade papillary carcinoma"). Seven (70%, 7/10) of those with follow-up (mean 21.6 years, range 7–30 years) and 28% (7/25) of the total cohort were found to have ipsilateral invasive carcinoma within 10 months to 24 years after the original biopsy (mean 9.7 years). Two patients died of metastatic disease, and two were alive but with known metastases (21). Similarly, Page and colleagues reported on a cohort of 28 women with "small, noncomedo" DCIS, followed for a mean of nearly 30 years, finding a 9-fold risk of invasive carcinoma over that time period compared to the general population (95% CI: 4.7–17). All cancers developed in the same breast and in the same region as the biopsy (22). The same investigators later expanded their cohort to include an additional 17 patients. In total, 16/45 (36%) developed invasive carcinoma in the same breast quadrant; 11 of the invasive cancers were diagnosed within 10 years, and the remainder were diagnosed between 12 and 42 years after the biopsy. Seven women developed distant metastatic disease, resulting in death (23).

Despite the limitations of such investigations, these studies not only demonstrate that untreated DCIS—including low-grade DCIS—is associated with later development of invasive malignancy, but also suggest that sufficiently long-term follow-up is essential for observing invasion.

Population-based Data: Detection, Recurrence, and Mortality

Investigating the impact of DCIS detection on the development of later ID offers circumstantial evidence for progression pathways. For example, if DCIS leads to ID, then detection of DCIS should theoretically lead to a decrease in interval cancers (cancers presenting between screening exams). Duffy and colleagues found exactly this result in their analysis of the association between DCIS and interval cancers (24). The authors evaluated aggregated data from 84 screening units in the United Kingdom. They assessed patient-level invasive interval cancer data arising in the 36-month period after screening (standard screening round length in the UK) with DCIS detection rates as continuous and categorical variables. In total, data from 52 436 568 women were included in the study. Screen-detected DCIS occurred with an average frequency of 1.6/1000 women screened (range 1.54–3.56/1000 women). There was a significant negative association of screening-detected DCIS cases with invasive interval cancer rates (Poisson regression coefficient -0.084 [95% CI: -0.13–0.03]; $P = 0.02$). For units with at least 1–2.22 cases of DCIS per 1000 women screened, for every three screen-detected DCIS cases, there was one fewer interval cancer in the next three-year period, an association that remained even after adjusting for small screen-detected invasive cancers and grade 3 invasive cancers.

Population data also suggests that women with screening-detected DCIS have a higher long-term risk of developing invasive breast cancer and higher mortality rates than women in the general population, even after undergoing treatment. A study of 35 024 women with screening detected DCIS followed between 5 and 20 years found an overall incidence rate of ID of 8.82 (95% CI: 8.45–9.21) per 1000 women per year, more than double the national (UK) cancer incidence rate of 2.52 (95% CI: 2.41–2.63) per 1000 women per year (25). Death rates in this group were 7% higher than the national breast cancer mortality rates, and women who were more intensely treated had lower rates of invasive cancer.

Other trials have demonstrated that there are higher recurrence rates in women treated only with excision. In the United Kingdom/Australia/New Zealand (UK/ANZ) trial of tamoxifen and radiotherapy for DCIS, for example, patients received either tamoxifen, radiotherapy, or both after local excision. A control group received complete local excision only (26). Despite complete local excision, 32% of the control group patients experienced a breast event (development of DCIS or ID) in the following 12 years. This again suggests the propensity of DCIS to progress to invasion.

Importantly, specific populations may be at the highest risk of mortality. Narod and colleagues looked at 108 196 women in the Surveillance, Epidemiology, and End Results 18 registries database who were diagnosed with DCIS and who later had a second primary breast cancer (follow-up mean 7.5 years, range 0–23.9 years) (27). Risk of dying was compared to that of women in the general population. Although breast cancer–specific mortality was relatively low—3.3% (95% CI: 3.0%–3.6%)—mortality was higher for women who received a diagnosis at a younger age (<35 years) (7.8% vs 3.2%; HR, 2.58 [95% CI: 1.85–3.60]; $P < 0.001$) and for Blacks versus non-Hispanic Whites (7.0% vs 3.0%; HR, 2.55 [95% CI: 2.17–3.01]; $P < 0.001$). The findings suggest the importance of assessing both screening and treatment strategies for women in certain demographic groups.

Modeling Studies

Given the difficulty of assessing DCIS progression through direct observation, modeling studies are a means of exploring the effects of screening and DCIS detection on mortality. The Cancer Intervention and Surveillance Modelling Network (CISNET) is a group of National Cancer Institute investigators who develop models to evaluate cancer screening and prevention. Five breast cancer CISNET models include DCIS. In addition, other non-CISNET models also incorporate DCIS into their respective frameworks (28). Models differ in methodologies (eg, Markov analytical models versus simulation models) as well as in source data, which ranges from national population screening data to U.S. Surveillance, Epidemiology, and End Results data to public pathology databases. There are equally varied assumptions regarding detectability, progression, regression, and even incidence of DCIS (28,29). For example, only some models assume a preclinical screening detectable DCIS stage necessarily precedes invasion, an assumption that leads to higher rates of progression than when this is not the case (61%–91% vs 20%–24.4%) (28,30,31). Several models allow for the possibility that DCIS may regress or return to an undetectable state (32,33). One recent overview of CISNET approaches toward DCIS suggests that given variable estimations in DCIS-related input parameters—from incidence to progression rates— it may be most optimal to evaluate a variety of models and results (28).

Trials

Overdiagnosis describes screen-detected cancers that might not otherwise be apparent clinically during the patient's lifetime; it is important to realize that overdiagnosis is not unique to breast cancer screening. A patient might theoretically undergo unnecessary treatment with associated potential morbidity for something that would never have undergone clinically impactful progression. In a 2017 article, Hendrick makes a distinction between obligate or type 1 overdiagnosis rates (cancers detected at screening that are not the cause of patient mortality) versus nonobligate or type 2 overdiagnosis

rates (detected cancers that never would have progressed or even regressed, for which there is only unconvincing evidence) (34–36). Estimates of overdiagnosis vary widely—0%–75% in the literature—but when properly adjusted for both lead time (the time of detection at screening vs the time the disease would have clinically presented and been diagnosed) and also patient risk, they are notably lower: 1%–10% (34,37). Hendrick notes that type 1 overdiagnosis rates are dependent on and increase by age at screening and calculates a rate of 9% for DCIS in women screening in the United States (34).

The drive to address overdiagnosis concerns—specifically overtreatment of accurate diagnosis—and to determine whether all DCIS mandates excision has been the impetus for several clinical trials: COMET (Comparison of Operative to Monitoring and Endocrine Therapy Trial for Low-risk DCIS) in the United States, LORD (Low-risk DCIS Trial) in Europe, LORIS (Low-Risk DCIS Trial) in the UK, and LORETTA (single-arm confirmatory trial of endocrine therapy alone for estrogen receptor-positive, low-risk ductal carcinoma in situ of the breast) in Japan (38–42). In addition, the LARRIKIN (Low And Intermediate Risk ductal carcinoma in situ study) trial has been proposed in Australia and New Zealand (Table 1) (43). As an aside, "larrikin" is an Australian term for a maverick or a person who disregards convention.

COMET, LORD, and LORIS are all phase III, prospective, randomized trials comprising two arms: treatment (surgery plus or minus adjuvant radiation) or active surveillance. LORETTA is a single-arm phase III trial without blinding or randomization in which patients with low-risk DCIS receive endocrine therapy during active surveillance. LORD and COMET allow the option of endocrine therapy in the treatment arm, while COMET also allows for endocrine therapy in the active surveillance arm.

Primary endpoints for COMET, LORD, and LORETTA are ipsilateral invasive breast cancer (IBC) over varying times (Table 1). For LORIS, the 10-year endpoint is ipsilateral IBC-specific survival. Some secondary endpoints of the four trials include progression to high-grade DCIS, contralateral invasive cancer rate, time to failure of active surveillance, mastectomy rate, invasive cancer-free survival, and overall survival.

To be included in the trials, women must have screening-detected calcifications and "low-risk" DCIS, the definition of which varies (Table 1). COMET also includes atypical ductal hyperplasia suspicious for DCIS given the overlap along the same disease spectrum. Only LORETTA restricts DCIS size to <2.5 cm, whereas two biopsies are needed for a calcification span of >4 cm in COMET, without a size cutoff. All four trials exclude DCIS associated with a mass on imaging or exam, personal history of IBC or DCIS, and synchronous contralateral IBC. Only COMET allows patients at high risk for breast cancer, those with multifocal DCIS, and patients with positive margins after lumpectomy for DCIS to participate.

LORD and LORETTA depend on local institutions for pathology review. LORIS uses real-time central histopathology review by expert DCIS pathologists. COMET requires consensus from two local pathologists.

Whereas COMET, LORD, LORIS, and LORETTA are trials in progress, LARRIKIN is a proposed study. Briefly, the primary endpoint is ipsilateral IBC or higher-grade DCIS than at biopsy at 5 years with inclusion of grade I asymptomatic, screening-detected DCIS, 2 cm or less in size. In addition, estrogen and progesterone receptor positivity and HER2 nonamplification are required. Exclusion criteria are history of DCIS or IBC, current IBC, Paget's disease, lobular carcinoma in situ, or *BRCA* mutation (43).

There are several potential flaws with the trials. Several studies have shown the potential for undersampling during core-needle biopsy when DCIS grade is initially determined (43–45). In one retrospective analysis of 296 patients meeting LORIS eligibility criteria, 20% were upgraded to invasive cancer at excisional biopsy (44). Grimm and colleagues also demonstrated upstaging to invasive disease, with a 7% rate for LORIS criteria patients (5/74), 6% for COMET (5/81), and 10% for LORD (1/10) (46). A recent 10-year single-institution retrospective analysis of 858 women found a 12% upgrade rate to invasive disease via COMET criteria (60/498), 5% via LORD (5/101), and 11.1% via LORIS (38/343) (47). Some have therefore argued for including calcification size and morphology in trial criteria, since these factors are predictive of invasion (43).

Another potential concern with study design arises from the many years low-grade DCIS may take to progress to invasive carcinoma (43,48–50). As well, DCIS treated with surgery still carries a 6% risk of invasive recurrence at 10 years (51). This has implications for follow-up in the current trials, because 5- to 10-year intervals are likely to underestimate the rate of progression (43).

Other important critiques focus on histopathologic approaches. As discussed above, it is well known that there is low agreement among pathologists regarding the grade of DCIS, especially between low- and intermediate-grade DCIS as well as atypical ductal hyperplasia and DCIS (52). To solve the problem of inter-pathologist agreement on the grade of DCIS, LORIS employs centralized histopathology review. However, proponents of LORD argue that local pathology review is more reflective of real-life DCIS management (40). Biomarkers may also confer relevant prognostic information, but they are not required components of all the trials (43). Some have argued for the role of Oncotype DX in trial inclusion and/or exclusion criteria, because studies have shown that a proportion of low- and intermediate-grade DCIS has a high risk of recurrence and progression (53–55).

The trials' definition of active surveillance can also pose a potentially confounding problem, with mandatory inclusion of endocrine therapy in LORETTA and the option to do so in COMET. Finally, low recruitment has been cited as a limitation to the trials—with factors such as limited resources at recruitment sites and long-held beliefs about standard DCIS treatment cited as possible reasons. For example, the

Table 1. Summary of Current and Proposed Low-risk Ductal Carcinoma In Situ (DCIS) Active Surveillance Trials

	LORD (35)	LORIS (36)	LORETTA (37)	COMET (34)	LARRIKIN (39)
Trial design/phase	RCT, Phase III	RCT, Phase III	Single-arm trial, Phase III	RCT, Phase III	Proposed RCT
Follow-up period	10 years	10 years	5 years	2, 5, 7, and 10 years	
Primary outcome	Ipsilateral invasive cancer-free rate	Ipsilateral invasive cancer-free survival time	Cumulative incidence of invasive ipsilateral cancer >1 cm	Ipsilateral invasive cancer rate	
Inclusion criteria					
Minimum age	45 years	46 years	40 years	40 years	55 years
Calcification detection	Screening	Screening	Screening	Screening or DCIS with +margins s/p lumpectomy	Screening or incidental
Biopsy	VACB	VACB or surgical	VACB or CB	VACB or surgical	
Size of DCIS	Any	Any	2.5 cm or less	Any; two site biopsy if >4 cm	2.0 cm or less
Location	Unilateral	Unilateral or bilateral	Unifocal and Unilateral	Unilateral, bilateral, or multifocal	
Nuclear grade	Low	Low + intermediate[a]	Low + intermediate	Low + intermediate	Low + intermediate
Comedonecrosis	No	No	No	Yes	No
Biomarkers	n/a	n/a	High ER+, HER2-	ER/PR ≥10%, HER2-[b]	ER/PR+, HER2-
Exclusion criteria					
Associated imaging findings	Mass, density, distortion, or stellate lesion	Mass	Mass	Mass	
Physical exam	Paget's, palpable mass, nipple discharge	Ipsilateral bloody nipple discharge, unless proven ductal ectasia	Palpable mass	Palpable mass, bloody nipple discharge, skin changes	
Breast cancer	History of IBC/DCIS	History of IBC/DCIS	Simultaneous or metachronous double cancer	History of IBC/DCIS	
Other cancer	Excluded except cervical in situ and basal cell	n/a	Uterine cancer	n/a	
Family history/high risk for breast cancer	Excluded unless tested negative for known family mutation	Excluded	*BRCA* mutation+ excluded	Included	
Treatment	Lumpectomy or mastectomy, +/- RT, +/- ET	Surgery + standard adjuvant therapy	None	Surgery + RT, +/- ET	
Active surveillance	Annual MMG	Annual MMG	Biannual MMG + US for first year, then annual, plus ET × 5 years	Biannual MMG +/- ET	
Pathology review	Local facility	Real-time central review	Local facility	Two-pathologist local consensus	

Table 1. Continued

	LORD (35)	LORIS (36)	LORETTA (37)	COMET (34)	LARRIKIN (39)
Recruitment start	2017	2014	2017	2017	proposed
Study origin and sites	The Netherlands, multiple European countries, 28 sites	UK, multicenter, 60 sites	Japan, multicenter	United States, multicenter, 80 sites	Australia and New Zealand
Enrolled/target enrollment[c]	33/1240	pending/188 (932)[d]	unknown/340	253/1200	550 (proposed)

Abbreviations: CB, core biopsy; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IBC, invasive breast cancer; MMG, mammogram; PR, progesterone receptor; RCT, randomized controlled trial; RT, radiation therapy; US, ultrasound; VACB, vacuum-assisted core biopsy.

[a]LORIS includes non-high-grade DCIS.

[b]HER2 0, 1+, or 2+ by immunohistochemistry if tested.

[c]As per publicly available information at the time of writing this review.

[d]Original target enrollment in LORIS was 932, which was changed to 188. Recruitment now closed. However, final enrollee number not yet publicly reported as of time of writing.

initial LORIS target enrollment was 932 with an altered target of 188 patients and expansion to 60 sites in an attempt to increase trial access (56). The trial is now closed for recruitment.

Clinical Predictors of Progression

Although there is an imperfect understanding of which cases of DCIS are more prone to progress, histopathologic and receptor characteristics such as larger size, estrogen receptor negative disease, and higher cytologic grade have all been linked to a greater likelihood of progression, as have extent of disease and symptomatic presentation (57). As described above, patient demographics—younger age and Black race, for example—have also been associated with a greater likelihood of ID and increased mortality (27). Clinical tools do exist to predict risk and likely outcomes of individual patients with DCIS, helping to assess appropriate treatment and, in particular, the value of radiotherapy. The Oncotype DX DCIS (Genomic Health, Redwood City, CA), for example, includes a 12-gene panel assay (7 cancer genes and 5 reference genes), producing a DCIS-scaled score from 0 to 100 (low risk <39; intermediate risk 39–54, high risk ≥ 55). The score predicts 10-year risk of ipsilateral local or invasive recurrence after lumpectomy. A recent analysis of the original Oncotype DX validation cohorts found that incorporating clinical variables such as tumor size and patient age at diagnosis increased the predictive capabilities for the risk of local recurrence (58,59). Cost-effectiveness of Oncotype DX for avoiding radiotherapy has not yet been demonstrated (59,60)

Conclusion

Despite the difficulty in directly observing the progression of in situ disease, and despite still-notable gaps in our understanding, a variety of approaches have helped to shed light on disease progression for DCIS. Animal models, population screening data, modeling studies, and "missed" biopsy studies all demonstrate that DCIS has the potential to progress to ID. Sufficiently long follow-up times are important in evaluating in situ progression. It is also worth emphasizing that certain clinical risk factors (Black race and young age, for example) have been shown to be associated with more aggressive disease. This supports the need for early evaluation of risk before women turn 30 to allow for appropriate screening as recommended in American College of Radiology guidelines (61). Finally, the rise of the surveillance DCIS trials demonstrates national and international interest in understanding the natural history of DCIS and will hopefully lead to improved treatment strategies.

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Conflict of Interest Statement

None declared.

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