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LOCAL-REGIONAL EVALUATION AND THERAPY (DM EUHUS, SECTION EDITOR)

Ductal Carcinoma In Situ Management: All or Nothing, or Something in between?

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Abstract

Purpose of Review Standard treatment for ductal carcinoma in situ (DCIS) is similar to that of invasive carcinoma. However, there is significant controversy regarding the true clinical implications of DCIS, and thus, the best management strategy. The aim of this review is to highlight relevant biology, diagnostic considerations, treatment options, and recent clinical trials.

Recent Findings Outcomes are generally excellent with low recurrence rates and exceptional disease-specific survival. Outcomes can be predicted using various prognostic indicators and/or nomograms to guide treatment decisions. Ongoing clinical trials of active surveillance are based upon the argument that *ipsilateral invasive recurrence* is the most clinically meaningful endpoint. These trials seek to compare ipsilateral invasive cancer diagnoses between standard of care and close monitoring.

Summary Recent trials have revealed the marked heterogeneity in the biology of DCIS, offering an opportunity to de-escalate therapy for women at lowest risk for progression. DCIS also presents an ideal setting in which to test novel prevention agents. Future care of patients with DCIS will include biomarker-based risk assessment in order to better individualize treatment to biologic risk of invasive progression.

Keywords Ductal carcinoma in situ · DCIS management · DCIS treatment · DCIS prognosis

Introduction

Carcinoma in situ is diagnosed in more than 60,000 women in the US each year, and over 80% of these cases consist of ductal carcinoma in situ (DCIS) [1]. The incidence of DCIS has been steadily rising over the past few decades [2] as women are living longer and more women are undergoing screening mammography [3, 4]. Risk factors for developing DCIS are similar to those for invasive breast cancer and include older age and a family history [4]. When DCIS is diagnosed on core needle biopsy, the risk of revealing invasive disease after excision is typically 10–20%, depending on the indication for biopsy and technique used [4–7]. However, there is significant controversy regarding the true clinical implications of a DCIS diagnosis, and thus, the best management strategy.

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DCIS Biology

DCIS can be defined as a neoplastic proliferation of ductal (epithelial) cells that are limited to the ducts of the breast and do not invade the stroma [8, 9]. Histological criteria from the College of American Pathologists are used to differentiate between three nuclear grades of DCIS using six morphological features, including pleomorphism, size, chromatin, nucleoli, mitoses, and orientation [10]. In general, low-grade DCIS is characterized by monotonous nuclei that may be up to 1.5–2 times the size of a red blood cell (RBC), while high-grade DCIS is often characterized by pleomorphic nuclei that are more than two times the size of an RBC with frequent mitoses and irregular chromatin (Fig. 1) [10]. This classification system for DCIS grading (G1: low nuclear grade; G2: intermediate nuclear grade; G3: high nuclear grade) is recommended by the AJCC [11]. In addition to grade, there are several architectural subtypes of DCIS, including cribriform, micropapillary, solid, and comedo types. DCIS can often be distinguished from invasive carcinoma by the presence of myoepithelial cells, which can be verified by

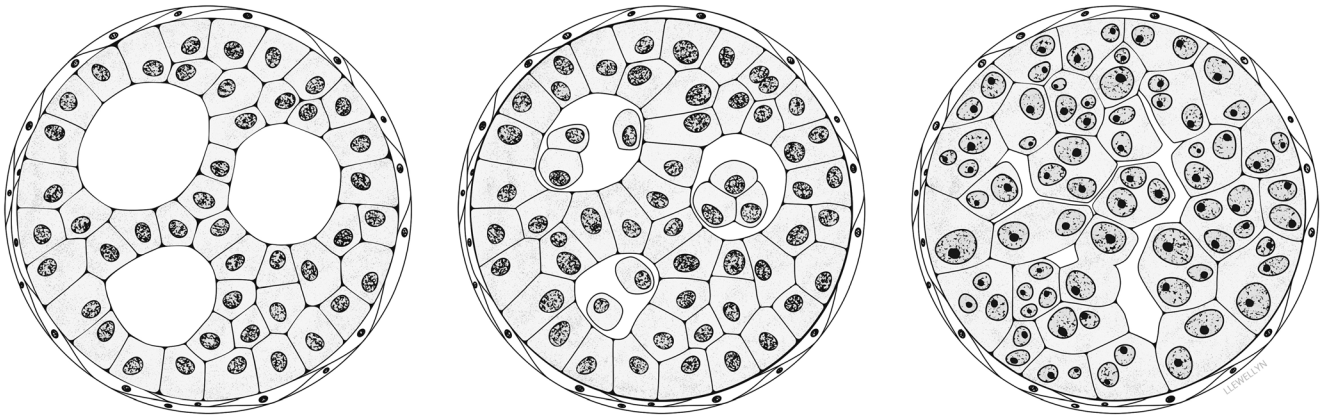

Fig. 1 Examples of ductal carcinoma in situ based on nuclear grade. Permission: Illustrated by Megan Llewellyn, MSMI, CMI; copyright Duke University; with permission under a CC BY-ND 4.0 license

multiple markers (e.g., calponin and p63) [12]. However, diagnosing DCIS remains a difficult challenge for many pathologists, and significant interobserver variability has been noted. Review of 73 DCIS specimens by > 100 pathologists demonstrated only 84% concordance [13]. Follow-up studies indicate that interpretive agreement by the same pathologists at two time points likely yields similar concordance rates [14].

Given that it is confined to the ductal system, DCIS is considered a "noninvasive" cancer and/or a nonobligate precursor to breast cancer. However, some studies have demonstrated genetic similarities between DCIS and invasive breast cancer [15–19]. In addition, the risk factors for DCIS have been shown to be similar to those for invasive carcinoma, including similar rates of germline BRCA1/2 mutations [20], further confirming the precursor nature of DCIS [21].

While the association between DCIS and invasive carcinoma appears strong, the exact progression from DCIS to invasive carcinoma is less understood, and only a few small studies describe the natural history of untreated DCIS. An early study of 28 women with low-grade DCIS that were inadvertently treated by biopsy alone were followed for > 30 years, and 16 women (36%) developed ipsilateral invasive breast cancers (same breast, same quadrant) resulting in 7 deaths from breast cancer [22]. In a review of publications related to the natural history of DCIS, the rate of progression ranged from 14 to 53% over 10+ years [23]. Undiagnosed DCIS in autopsy studies was also noted to be approximately 9% [23], suggesting a greater prevalence of DCIS than currently appreciated, although the clinical significance is likely negligible. A recent study of 720 patients with pure DCIS who underwent excision alone without radiation included 124 patients with < 1 mm margins (surveillance group) and 596 patients with ≥ 1 mm margins (excision group) [24]. The 10-year local recurrence (LR) probabilities (in situ or invasive) stratified by grade for the excision group ranged from 13 to 35%, while the rates for the surveillance group ranged from 51 to 70%. The 10-year LR rates for only invasive disease ranged from 8 to 17% for the excision group and 26–31% for the surveillance group [24]. Taken together, these findings confirm that there is a strong correlation between DCIS and progression to invasive carcinoma, and additional studies are needed to further define the potential timeline of this progression, including associated risk factors.

Imaging of DCIS

When considering management options for DCIS, it is important to not only categorize the disease (by grade and receptor status), but also to establish the extent of disease. On mammogram, DCIS often presents as calcifications (> 90% of cases [25]), which may have a distinct appearance compared to benign findings (Table 1) [34]. Given that the sensitivity of mammography decreases with increasing breast density, breast ultrasound is commonly used for women with dense breast tissue; however, it appears to have the lowest positive predictive value (PPV) for detecting DCIS [26]. Alternatively, breast MRI (magnetic resonance imaging) can be used as a screening or diagnostic tool with DCIS presenting as non-mass enhancement or an irregular mass [27].

Some studies suggest that MRI is the most sensitive imaging modality for diagnosing DCIS (high and intermediate grade, in particular [28, 35, 36]), and it may be more accurate in estimating size than mammography alone [27]. In a study of 99 patients found to have suspicious calcifications on screening mammogram (BI-RADS 4 or 5) who then underwent breast MRI, the PPV in detecting DCIS increased from 25% by mammography to 57% on MRI [29]. Similarly, Berg et al. demonstrated that MRI was more sensitive than mammography, but also noted a higher risk of

Table 1 Comparison of breast imaging modalities [26–29, 30•, 31, 32, 33•]

	Mammography	MRI	Ultrasound
Appearance of DCIS on imaging	Microcalcifications: amorphous, coarse, heterogeneous, fine pleomorphic; clustered, linear or segmental distribution	Non-mass enhancement: linear or clumped; mass	Microlobulated, cystic, or solid mass; mildly hypoechogenic; ductal extension/dilation
Sensitivity	27–80%	35–100%	49%
Specificity	79%	75%	Unknown
PPV	25–55%	57%	12.9%
NPV	97%	98%	Unknown
Size estimation (under or over)	Usually underestimates	May overestimate (low grade) or underestimate (high grade)	May overestimate

DCIS ductal carcinoma in situ, *PPV* positive predictive value, *NPV* negative predictive value

overestimation [26]. However, other studies have demonstrated an overall sensitivity of 27–80% for mammography and 35–100% for MRI [28, 30•, 31] (Table 1). For mammographic BI-RADS 4 lesions, MRI may be a useful noninvasive adjunct, although it may also lead to false-positive findings that require additional biopsies [32].

For patients diagnosed with DCIS, some have suggested routine preoperative MRI to identify additional disease. Petrillo et al. demonstrated 21.6% of patients in an institutional database of 245 DCIS patients who underwent preoperative MRI were found to have additional disease [36]. However, preoperative MRI has also been shown to be less accurate in predicting extent of disease in patients with extensive DCIS, and it may not alter mastectomy rates [37]. Additionally, Davis et al. demonstrated similar mastectomy and re-excision rates for women who did and did not undergo preoperative MRI [38].

Given the often multifocal and discontinuous growth pattern of DCIS, preoperative size estimation, and thus surgical planning, can be particularly challenging. When comparing imaging modalities, mammography appeared to be most accurate for low-grade DCIS but tended to underestimate intermediate and high-grade DCIS. In contrast, MRI overestimated low-grade DCIS, although it also underestimated high-grade DCIS (albeit to a lesser degree than mammography) [30•]. Currently, the NCCN (National Comprehensive Cancer Network) guidelines recommend only performing breast MRI when additional information is needed prior to initiating treatment, while recognizing that it is unlikely to improve outcomes [39••]. Furthermore, breast MRI has not been shown to reduce rates of local-regional recurrence (LRR) or contralateral breast cancer (CBC) [40].

Following surgery, post-excision mammography should also be considered when margin status and/or the presence of residual calcifications are uncertain [39••, 41]. Post-treatment surveillance is similar to that of women with invasive disease, including annual mammography, starting 6–12 months after completion of radiation therapy [39••, 42].

Surgical Management of DCIS

Current guidelines for the surgical management of biopsy-proven DCIS parallel those of invasive cancer, namely complete surgical excision to negative margins [39••]. This both removes known disease and may identify adjacent invasive disease, which may occur in up to 25% of patients [43]. While some have found a 20% risk of synchronous invasive carcinoma at surgical excision for low-risk DCIS [44•], others have demonstrated that it could be only 6–10% [45••, 46]. Given these variable findings, studies to identify a low-risk subgroup of patients to forgo primary surgical excision of DCIS are underway [47, 48•, 49•].

Complete surgical excision may be performed by breast-conserving surgery (BCS), classically with whole breast radiation therapy (WBRT), or by total mastectomy with generally similar recurrence risks and survival [4]. As there are no disease-specific survival advantages to mastectomy, individual surgical decision-making is often based on patient perspectives and motivations [50]. However, extensive DCIS based on imaging may require up-front mastectomy. When BCS is elected, the intent is to excise all known disease and associated calcifications, which often requires a localizing procedure such as a wire or radioactive seed. Intraoperative specimen radiograph is mandatory for real-time confirmation of retrieval of the intended target, as well as radiologic evaluation of margins. Re-excision of positive/close margins may be performed in those attempting BCS, with mastectomy reserved for those unable to obtain negative margins after multiple attempts. Prior to margin re-excision, post-lumpectomy mammography may be valuable in identifying residual calcifications associated with retained DCIS [41].

Surgical Margin Status

Three [48, 51, 52] of the four [53] early randomized DCIS trials defined an adequate margin width as microscopically clear margins ("no ink on tumor"). However, one notable

single-institution study found WBRT did not reduce ipsilateral breast tumor recurrence (IBTR) rates when the excised DCIS had a margin width of ≥ 1 cm, which many interpreted as wider margins being optimal for all DCIS [54]. Subsequently, significant practice variability existed with roughly one third of women undergoing a second surgical procedure to obtain "clear" and/or wider margins [55, 56]. As such, surgical margin guidelines were established in 2016, and the currently accepted pathological surgical margin for pure DCIS treated with BCS is 2 mm, regardless of planned adjuvant therapy [39••, 57•]. This margin definition notably differs from the consensus guidelines for invasive cancer (including any DCIS associated with invasive cancer), in which "no ink on tumor" is considered a permissible negative margin width [58].

Surgical Nodal Evaluation

As pure DCIS is a non-invasive process, theoretically, there is no potential for lymph node involvement. However, a study of 349 patients with pure DCIS who underwent lumpectomy and sentinel lymph node biopsy (SLNB), 94.6% were pN0, 3.4% were pN0i+ (ITCs), 1.7% were pNmi, and only a single patient had pN1 disease (0.3%) [59•]. As such, surgical lymph node evaluation is not routinely recommended for women with DCIS undergoing BCS, regardless of grade, size, or receptor status. However, when mastectomy is planned, SLNB should be strongly considered at the time of the index operation. Since patients who undergo mastectomy for DCIS generally have more extensive disease, they are more likely to harbor occult invasive disease. Moreover, since SLNB in the setting of mastectomy adds little morbidity, this approach is recommended.

Radiation Therapy for DCIS

The purpose of radiation therapy following surgical excision of DCIS is to eradicate residual, but undetectable disease in the conserved breast. Four notable trials, each enrolling approximately 1000 women with 10–20 years of follow-up, found a marked reduction in recurrence risk ranging from 38 to 59% with the addition of WBRT following lumpectomy [60–63]. A meta-analysis of these major multi-center trials found a pooled hazard ratio of 0.49 (HR 0.49, 95% CI 0.41–0.58), suggesting a clinically meaningful reduction in recurrence rates of 50% [51]. Furthermore, adjuvant radiation was found to reduce recurrence rates in all subgroups (regardless of age, grade, or margin status). However, none of these prospective, randomized trials identified a survival benefit with the addition of radiotherapy. In contrast, one population-based longitudinal cohort study found a statistically significant survival benefit in those receiving radiation, as compared to wide excision alone (1.8% vs. 2.1%, HR 0.73, 95% CI 0.62–0.88) in patients with higher nuclear grade, younger age, and larger tumor size [52].

In addition to WBRT, more recent studies have investigated various technical aspects of radiotherapy administered after BCS, while others have explored options for post-mastectomy radiation therapy (PMRT). In a retrospective analysis of > 4000 patients with DCIS from 10 academic institutions who underwent BCS with WBRT ± boost, the additional boost was shown to significantly decrease IBTR rates across all DCIS age groups, similar to the benefit observed in patients with invasive breast cancer [53]. Regarding hypofractionation, LR rates were similar among > 1600 women with DCIS treated with BCS and radiation using hypofractionated and conventional regimens [64]. The safety of these approaches has been further evaluated and validated in a recent meta-analysis, which confirmed that hypofractionated radiotherapy is safe, and the addition of a boost may further reduce the risk of LR [65].

Local control following mastectomy for DCIS is excellent with recurrence rates of 1–2% [4]. However, patients with close/positive margins following mastectomy for DCIS may be at a higher risk for LR. In a review of 810 mastectomy patients with DCIS, 11.7% had close/positive margins, 7.5% underwent PMRT, and none of the patients receiving PMRT had a LR [66]. On multivariate analysis, close margins were the only independent predictor of LR. The authors concluded that PMRT is not warranted, except for patients with multiple close/positive margins that cannot be surgically excised [66]. In contrast, another study evaluating close/positive margins post-mastectomy found the risk of chest wall recurrence was 1.7% at 8 years for the entire cohort, and 3.3% for those with high-grade disease. These authors concluded chest wall recurrence risk is sufficiently low not to warrant PMRT for close margins [67]. Taken together, national guidelines do not currently support routine use of PMRT for DCIS [39••].

Endocrine Therapy for DCIS

The estrogen and progesterone receptors (ER, PR) are the two most important biomarkers for DCIS and should be assessed to guide decision making for adjuvant endocrine therapy. Numerous large, randomized trials have shown a clear benefit to adjuvant endocrine therapy to reduce ipsilateral in breast events, as well as contralateral risk reduction. For example, NSABP B-24 enrolled > 1804 women with DCIS undergoing BCT and randomized them to placebo or tamoxifen [68]. At greater than 10 years of follow-up, the tamoxifen group had a significant reduction in invasive and non-invasive IBTR for an overall 3.4% absolute reduction in any IBTR ($p < 0.001$). The tamoxifen group similarly had a 3.2% ($p = 0.023$) absolute risk reduction in CBC [68]. Similar results were seen in a study of >

1701 women undergoing complete local excision, who were randomized to WBRT, tamoxifen, or both [63]. With greater than 10 years of follow-up, tamoxifen reduced the incidence of all new breast events (HR 0.71, $p = 0.002$), ipsilateral in-breast DCIS (HR 0.7, $p = 0.03$), and contralateral breast events (HR 0.44, $p = 0.005$). In contrast to the NSABP trial, they found no reduction in ipsilateral invasive breast events (HR 0.95, $p = 0.8$).

For post-menopausal women, aromatase inhibitors have been shown to be more effective in reducing invasive breast cancer recurrences when compared to tamoxifen; therefore, studies were designed to compare the efficacy of anastrozole to tamoxifen in hormone-receptor positive DCIS. In IBIS-II, nearly 3864 post-menopausal women were randomized to anastrozole or tamoxifen, and anastrozole was found to be non-inferior to tamoxifen with no difference in overall recurrence [69]. Similarly, the NSABP B-35 included 3104 post-menopausal women randomized to receive anastrozole or tamoxifen for 5 years [70•]. The anastrozole group had a significantly higher 10-year breast cancer-free interval (89.1% tamoxifen vs. 93.1% anastrozole).

In light of these trials, the NCCN recommends 5 years of adjuvant endocrine therapy for patients with hormone-receptor-positive DCIS treated with BCT or excision alone. Tamoxifen is the agent of choice for pre-menopausal women, while either tamoxifen or an aromatase inhibitor is acceptable for post-menopausal women based on age and other medical risk factors [39••].

DCIS Outcomes

LR rates for DCIS are estimated to range from 5 to 25%, depending on the tumor biology, treatment options, and follow-up period [71, 72]. In a study of 401 low-risk DCIS patients from a single institution who underwent surgical excision, the 10-year invasive IBTR rate was 5.3% overall (all BCS patients) and 6% for those omitting radiation [44•]. Similarly, in a population-based cohort of 1036 women with DCIS treated with BCS, the 5-year overall risk of recurrence was 8.2% for invasive cancer and 11.7% for DCIS [71]. In general, consistent risk factors for recurrence include younger age at diagnosis, positive surgical margins, tumor size and grade, and comedo necrosis [4]. Furthermore, the pathological characteristics of second breast cancers, including grade and ER status, tend to be similar to that of the index DCIS [73]. Regarding outcomes stratified by local-regional treatments, similar adjusted disease-specific survivals have been observed for patients undergoing mastectomy, lumpectomy with radiation, and lumpectomy alone [74].

Given these exploratory findings, multiple groups have attempted to identify prognostic risk factors and algorithms for predicting outcomes. One of the earliest schemas developed is the Van Nuys classification system, which combined nuclear grade and comedo-type necrosis to predict recurrence [75]. The groups included (1) non-high-grade DCIS without comedo necrosis, (2) non-high-grade DCIS with comedo necrosis, and (3) high-grade DCIS with or without comedo necrosis. Using these subgroups, LR rates were 3.8% in group 1, 11.1% in group 2, and 26.5% in group 3, with 8-year actuarial disease-free survival rates of 93%, 84%, and 61%, respectively [75]. The Van Nuys Prognostic Index was later refined and now uses a scoring system that quantifies five prognostic factors: tumor size, margin width, nuclear grade, age, and comedo necrosis [76].

Expanding on this concept, Van Zee and colleagues developed a nomogram to predict LR after BCS for DCIS based on 10 variables: age at diagnosis, family history of breast cancer, presentation (clinical and/or radiological findings), adjuvant radiation, adjuvant endocrine therapy, nuclear grade, necrosis, surgical margins, number of surgical excisions, and year of surgery [77, 78]. The DCIS nomogram demonstrated good calibration and discrimination for predicting 5- and 10-year LR probabilities (bootstrap corrected c-index 0.688) [77], and it was subsequently externally validated in multiple populations (c-indices 0.66–0.68) [79–81].

Beyond ipsilateral events, patients with DCIS may also experience CBC and/or distant recurrences. Based on data from 23,547 women with DCIS in the California Cancer Registry, the risk of CBC (in situ and invasive disease) was significantly higher for women with DCIS compared to the general population [82]. In a recent study of DCIS patients in the SEER (Surveillance, Epidemiology, and End Results) database, ER-positive DCIS was shown to be associated with CBC risk [83], suggesting that it may actually represent a field defect similar to that of other types of breast atypia. In a separate population-based cohort of 1492 women with an initial diagnosis of DCIS treated with BCS alone, the overall 10-year risk of regional/metastatic invasive cancer was 3.8%, although it ranged from 1.2 to 22.5% in various subgroups [84].

Regarding survival, review of 108,196 women with DCIS in the SEER database (mean follow-up 7.5 years) demonstrated that the 20-year breast cancer-specific mortality was 3.3% overall [85••]. However, it was higher for women diagnosed before age 35 years (compared to older women) and for blacks (compared with non-Hispanic whites). The risk of death was significantly higher following an ipsilateral invasive breast cancer recurrence. Interactive decision aids are being developed to help patients assess the risks and benefits of treatment, with tools designed to present clinical trial data in a patient-facing manner (https://dcisoptions.org/dst). Additional research is necessary to effectively communicate risk in order to promote informed decision making around treatment options.

DCIS Molecular Risk Predictors

Researchers have long sought to identify either imaging or tissue-based markers to stratify risk in DCIS. Currently, there are two multiplex molecular classifiers in clinical use. The DCIS Score is a 12-gene expression RT-PCR (reverse transcription polymerase chain reaction) assay for DCIS that estimates the 10-year risk of any LR (DCIS or invasive) following BCS without radiation [86]. Among 327 patients in the ECOG 5194 registry study of excision alone for low-risk DCIS, the DCIS Score was shown to correlate with LR risk. For DCIS risk groups (low, intermediate, and high), the 10-year risk of an ipsilateral breast event was 10.6%, 26.7%, and 25.9%, respectively. For invasive cancer events, it was 3.7%, 12.3%, and 19.2%, respectively [86]. The prognostic value of the DCIS Score was confirmed in a large population-based cohort of 3320 patients, which correlated the DCIS Score with LR (low: 12.7%, intermediate: 33%, high: 27.8%), albeit with less discrimination compared to the ECOG 5194 dataset [86, 87]. As follow-up to this study, the investigators combined the ECOG 5194 and Ontario cohorts and found that the DCIS Score, age at diagnosis, tumor size, and year of diagnosis were all independently associated with 10-year LR risk [88•]. Combining clinical factors with the DCIS Score was able to provide improved risk stratification over the DCIS Score alone.

A new molecular tool, the DCISionRT Test, is based on 7 IHC (immunohistochemical) markers (COX-2, FOXA1, HER2, Ki-67, p16/INK4A, PR, and SIAH2), as well as four clinicopathologic features (age, size, margin status, and palpability). This biological signature has been validated in two separate datasets, and interestingly, appears to be correlated with the risk of invasive recurrence [89•]. For patients treated without RT, the DCISionRT Test identified a low-risk group with a 10-year invasive cancer risk of 4% and a high-risk group with an invasive cancer risk of 15%. This tool is starting to be used clinically, although it remains to be seen how it compares to the DCIS Score with respect to patient and provider uptake.

Clinical Trials for DCIS

Recent clinical trials have discovered the marked biologic heterogeneity among patients with DCIS, offering an opportunity to de-escalate therapy for those at lowest risk for progression. RTOG 9804 was a study of "good risk" DCIS, defined as low- or intermediate-grade DCIS, measuring up to 2.5 cm. Patients were randomized to either surveillance or radiation; both arms allowed adjuvant tamoxifen. At a median follow-up of 7 years, the ipsilateral LR rate was 0.9% among women with radiation, compared to 6.7% among those without radiation (HR 0.11; 95% CI, 0.03–0.47) [90]. Unpublished data at a longer median follow-up of 12.4 years showed that the cumulative incidence of any LR was 2.8% for those in the WBRT arm and 11.4% for those in the observation arm (HR 0.26, 95% CI 0.13–0.54).

The most recent trials for DCIS are based upon the argument that only *ipsilateral invasive recurrence*, rather than *any recurrence*, is the most clinically meaningful endpoint and the only one that justifies aggressive local-regional treatment. These trials seek to compare ipsilateral invasive cancer diagnoses between two treatment strategies—standard of care where all DCIS is excised, compared to close monitoring where only those with DCIS that progress are treated aggressively. The strategy is based upon similar trials for early stage prostate malignancies, which changed the treatment paradigm for patients diagnosed with screen detected prostate cancer [91]. There are three trials currently recruiting, all of which randomize patients with low-risk DCIS to guideline concordant care or active monitoring. The LORIS trial is recruiting in the UK [92], the LORD trial in Europe [48], and the COMET trial in the US [93] (Table 2). Although the trials differ slightly with respect to eligibility criteria and follow-up schedules, they are sufficiently similar to allow for a meta-analysis of results when all three trials have met their primary endpoints. Furthermore, comprehensive biospecimen collection in all three trials will allow for discovery of new biomarkers specific for *invasive progression*, rather than any recurrence.

Finally, DCIS and other preinvasive lesions present an ideal opportunity in which to test novel prevention agents using a window of opportunity trial design with biomarker endpoints. Ongoing trials are evaluating the possible role of immune-modulating agents (e.g., pembrolizumab, dendritic cell vaccine, Neu/Vax), novel targets (e.g., JAK/STAT inhibition, others), as well as novel endocrine therapies (e.g., topical tamoxifen, bazedoxifene) to establish proof of concept in support of larger-scale prevention studies (Table 2).

Conclusions

DCIS is a biologically heterogeneous group of lesions which are associated with variably increased risks for invasive cancer. Currently, DCIS continues to be treated with local-regional therapies that are similar to those recommended for invasive cancer. Guidelines for both loco-regional and systemic treatment for DCIS are well described, based upon randomized trials. However, given the heterogeneity of DCIS, there may be a group that could be safely managed with close monitoring, such as that recommended for atypical ductal hyperplasia, and others that may require additional targeted therapies such as immune modulation. International efforts aimed towards more precise risk assessment of DCIS will allow for greater individualization of treatment options for future patients.

Table 2 Open clinical trials related to the management of ductal carcinoma in situ. Study information obtained from ClinicalTrials.gov website accessed 11/15/2018 [94••]

Identifier(s), contact/PI	Title	Phase	Drug/intervention
NCT02926911 AFT-25 PI: Shelley Hwang (Duke University)	Comparison of Operative to Monitoring and Endocrine Therapy (COMET) Trial for Low Risk DCIS	III	Other: Guideline concordant care Other: Active surveillance
LORIS PI: Matthew Wallis (University of Birmingham, UK)	LORIS: A phase III Trial of Surgery versus Active Monitoring for Low Risk DCIS	III	Other: Active monitoring Other: Surgery ± RT, ± hormone therapy
NCT02492607 LORD EORTC-1401 PI: Jelle Wesseling (The Netherlands Cancer Institute)	Management of Low-risk DCIS (LORD): The LOw Risk DCIS study	III	Other: Standard treatment Device: Digital mammography Radiation: Radiotherapy
NCT02993159 PI: Seema Khan (Northwestern University)	Testing an Active Form of Tamoxifen (4-hydroxytamoxifen) Delivered Through the Breast Skin to Control Ductal Carcinoma in Situ (DCIS) of the Breast	II	Drug: Afimoxifene Other: Laboratory biomarker analysis Other: Placebo Drug: Tamoxifen citrate
NCT03535506 PI: Paula Pohlmann Georgetown University	Preoperative Palbociclib in Patients with DCIS of the Breast that are Candidates for Surgery	II	Drug: Palbociclib
NCT00256217 PI: Rita Mehta (Chao Family Comprehensive Cancer Center)	Chemoprevention Trial – Anastrozole in Ductal Carcinoma In Situ (DCIS) in Post-Menopausal Women	II	Drug: Anastrozole
NCT02061332 PI: Brian Czerniecki (University of Pennsylvania)	DC Vaccine for patients with Ductal Carcinoma In Situ	I/II	Biological: HER2 pulsed dendritic cell vaccine
NCT02694809 PI: Swati Kulkarni (Northwestern University)	The PROMISE Study: Duavee in Women with DCIS	II	Drug: Conjugated estrogens/bazedoxifene Other: Laboratory biomarker analysis Other: Pharmacological study Other: Placebo Procedure: Quality of life assessment Other: Questionnaire administration
NCT02352883 ECOG-E4112 PI: Constance Lehman (ECOG-ACRIN Cancer Research Group)	MRI and Gene Expression in Diagnosing Patients with Ductal Breast Cancer in Situ	n/a	Procedure: MRI Other: Quality of life assessment Other: Laboratory biomarker analysis Other: Cytology specimen collection
NCT00470236 TROG 07.01 Study Chair: Boon Chua (Prince of Wales Hospital Randwick)	Radiation Doses and Fractionation Schedules in Non-low Risk Ductal Carcinoma in Situ (DCIS) of the Breast	III	Radiation: Standard WB fractionation Radiation: Shorter WB fractionation Radiation: Standard WB fractionation + Boost Radiation: Shorter WB fractionation + Boost
NCT00907868	Breast-Conserving Surgery and Whole-Breast Radiation Therapy with or without Additional	III	Radiation: Partial breast irradiation Radiation: Whole breast irradiation

Table 2 (continued)

Identifier(s), contact/PI	Title	Phase	Drug/intervention
PI: David Azria (Institut du Cancer de Montpellier – Val d'Aurelle)	Radiation Therapy to the Tumor in Treating Women with Ductal Carcinoma in Situ (BONBIS)		
NCT00072462 IBIS-II DCIS Study Chairs: Jack Cuzick (Queen Mary University of London); Anthony Howell (University of Manchester)	Adjuvant Tamoxifen Compared with Anastrozole in Treating Postmenopausal Women with Ductal Carcinoma in Situ	III	Drug: Tamoxifen citrate Drug: Anastrozole
NCT00003857 RTOG-98-04 Study Chairs: Beryl McCormick (Memorial Sloan Kettering Cancer Center); Barbara Smith (Massachusetts General Hospital); Timothy Whelan (Margaret and Charles Juravinski Cancer Centre)	Radiation Therapy with or without Optional Tamoxifen in Treating Women with Ductal Carcinoma in Situ	III	Drug: Tamoxifen citrate Procedure: Adjuvant therapy Radiation: Radiation therapy
NCT02389699 PI: Liao Ning (Guangdong Academy of Medical Sciences)	Comparison of Intra-operative Radiotherapy with Post-operative Radiotherapy for Women with Ductal Carcinoma in Situ	n/a	Radiation: Intraoperative radiotherapy Radiation: Whole breast radiation
NCT02766881 OCOG-2016-DUCHESS PIs: Eileen Rakovitch (Sunnybrook Health Sciences Odette Cancer Centre); Tim Whelan (Juravinski Cancer Centre)	Evaluation of the DCIS Score for Decisions on Radiotherapy in Patients with Low/Intermediate Risk DCIS	n/a	No intervention (observational)
NCT03216421 PI: Eileen Connolly (Columbia University)	Intraoperative Radiation Therapy (IORT) in DCIS	n/a	Other: Quality of life questionnaires
NCT02908178 PCORI-SW-1 PI: Shi-Yi Wang (Yale University)	Comparative Effectiveness of Sentinel Lymph Node Biopsy for Ductal Carcinoma in Situ	n/a	Procedure: Sentinel lymph node biopsy (SLNB)
NCT03543397 PI: Marie Noelle Roedlich (University Hospital, Strasbourg, France)	MRI in Ductal Carcinoma in Situ (DCIS)	n/a	No intervention (observational)
NCT03148015 PI: Richard Hoefer (Sentara Norfolk General Hospital)	Novel Molecular Targets for Ductal Carcinoma in Situ (DCIS)	n/a	Other: Biomarkers (observational)
NCT02936999 PI: Mary Wilkinson (Inova Schar Cancer Institute)	Vitamin D Supplementation in Women with DCIS and/or LCIS	n/a	Drug: Cholecalciferol (interventional, single group assignment)
NCT02872025 PI: Laura Esserman (University of California, San Francisco)	Pembrolizumab in High-risk Ductal Carcinoma in Situ (DCIS)	I	Drug: Pembrolizumab
NCT03375801 PI: Liesbeth Boersma (Maastricht University) Location: Netherlands	Implementing a Decision Aid for Breast Cancer and DCIS Patients Deciding on Their Radiation Treatment	n/a	Other: Decision aid (interventional, non-randomized sequential assignment)

Table 2 (continued)

Identifier(s), contact/PI	Title	Phase	Drug/intervention
Sponsor/Collaborator: Maastricht University			
NCT03495011 PI: Habibollah Rahbar (University of Washington)	MRI Characterization of Mammographically Detected DCIS	n/a	Diagnostic test: Breast MRI Other: Laboratory biomarker analysis (observational)
NCT02389673 PI: Liao Ning (Guangdong Academy of Medical Sciences)	Intra-operative Radiotherapy for Women with Ductal Carcinoma in Situ Breast Cancer	n/a	Device: Intraoperative radiotherapy (interventional, randomized, parallel assignment)
NCT02617082 PI: Xiaoli Yu (Fudan University)	Partial Breast Irradiation for Low-risk Ductal Carcinoma in Situ after Breast-conserving Surgery	II	Radiation: Partial breast irradiation
NCT02636582 PI: Elizabeth Mittendorf (MD Anderson Cancer Center)	Nelipepimut-S Plus GM-CSF Vaccine Therapy in Treating Patients with Breast Cancer	II	Other: Laboratory biomarker analysis Drug: Nelipepimut-S plus GM-CSF vaccine Biological: Sargramostim
NCT01439711 CALGB-40903 PI: Shelley Hwang (Duke University)	Letrozole in Treating Postmenopausal Women with Ductal Carcinoma in Situ	II	Drug: Letrozole Procedure: MRI Procedure: Conventional surgery

PI principal investigator, *DCIS* ductal carcinoma in situ, *RT* radiation therapy, *HER2* human-epidermal-growth-factor-receptor-2, *MRI* magnetic resonance imaging, *WB* whole breast, *N/A* not applicable

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Compliance with Ethics Guidelines

Conflict of Interest Jennifer Plichta, Laura Rosenberger, Cosette DeChant, and E. Shelley Hwang declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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