Updates on treating ductal carcinoma *in situ*: what's to know in 2021

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Purpose of review
Ductal carcinoma *in situ* (DCIS) is a noninvasive stage of disease but understood to be a nonobligate precursor to invasive breast cancer. As such, women with DCIS are routinely recommended for standard breast cancer treatment to prevent progression to invasive disease. DCIS, however, represents a heterogeneous group of lesions that differs in its biologic behavior and risk of progression. Thus, optimal treatment is unclear. This review presents the clinical trials evaluating the de-escalation of therapy, attempts at risk stratification, and future directions in the management of this disease.

Recent findings
The de-escalation of therapy for patients with DCIS is being actively explored. Although no group of patients based on clinicopathologic features has yet been identified as suitable for omission of therapy, molecular tests appear better able to stratify patients at low risk for whom omission of radiation may be considered. Trials considering omission of surgery are ongoing, and the use of Herceptin and vaccine therapy are also being explored.

Summary
The current review provides a centralized summary enabling the clinician to better understand the complexity of DCIS and the controversies over the optimal management of this disease. It highlights the need for better risk stratification to individualize patient care.

Video abstract
http://links.lww.com/COOG/A77.

Keywords
breast cancer, de-escalation of therapy, ductal carcinoma *in situ*, omission of surgery, radiotherapy

INTRODUCTION

Ductal carcinoma *in situ* (DCIS), or stage 0 breast cancer, is defined by neoplastic breast cells confined to the lining of the breast ducts and is considered a noninvasive stage of breast cancer. As such, there is no risk for distant metastases or death. Currently, DCIS comprises up to 20% of breast cancers diagnosed in the United States, which is the direct result of widespread screening mammography [1]. More than 90% of DCIS cases are diagnosed by routine screening.

Although noninvasive, DCIS is considered a nonobligate precursor to invasive breast cancer. Small, retrospective natural history studies have suggested that DCIS progresses to invasive breast cancer in 14–53% of patients over a follow-up of 15–25 years [2,3]. Therefore, treatment for DCIS centers on the prevention of invasive disease. However, many DCIS lesions appear never to progress to invasive cancer such that the optimal clinical management of this noninvasive stage of disease is unclear.

Given the uncertainty about the true risks of DCIS, uniform and standard treatment may constitute overtreatment for some. This review focuses on the current efforts to recognize the heterogeneity of this disease and to stratify patients according to risk of development of invasive disease. Current clinical trials evaluating the de-escalation of therapy for patients with DCIS are also presented.

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KEY POINTS

- DCIS is a noninvasive stage of breast cancer associated with excellent survival.
- Current treatment protocols for this heterogenous disease may constitute overtreatment for some.
- As with invasive cancer, studies are underway evaluating de-escalation of therapy.
- Future studies focused on better risk stratification using molecular signatures and artificial intelligence methods are necessary to improve clinical decision-making.

STANDARD THERAPY FOR DUCTAL CARCINOMA *IN SITU*

Current standard therapy for DCIS includes breast conservation therapy (BCT) or mastectomy with consideration of endocrine therapy for additional risk reduction. BCT includes a lumpectomy with negative margins followed typically by radiation. Although BCT has largely replaced mastectomy as the standard surgical approach for patients with DCIS, some believe that surgery and radiation may still represent overtreatment for select patients with this stage of disease.

EFFICACY OF WHOLE BREAST RADIOTHERAPY

Radiation therapy has been well established as effective adjuvant therapy for the reduction of breast cancer recurrence after lumpectomy for patients with DCIS. The efficacy of whole breast radiotherapy (WBRT) in reducing ipsilateral breast tumor recurrence (IBTR) has been demonstrated in four randomized clinical trials [4–7]. Among 3725 women who underwent surgical excision for DCIS, the rate of IBTR ranged from 19 to 30% among women who did not receive radiation therapy and was reduced to 9–15% in those who did. A meta-analysis confirmed that the addition of radiation therapy reduced the absolute 10-year risk of IBTR by 15.2% (12.9 versus 28.1%) compared with surgery alone [8]. Radiotherapy was effective regardless of age at diagnosis, extent of surgery, use of tamoxifen, margin width, DCIS grade, size of lesion, or presence of necrosis. Even in women with small lesions that were low-grade and excised with negative margins, an 18% absolute reduction in 10-year IBTR was realized with the addition of radiation therapy. Current NCCN guidelines therefore recommend adjuvant WBRT for patients with DCIS following lumpectomy.

Despite the demonstrated efficacy of radiation therapy in reducing both DCIS and invasive recurrence after lumpectomy, there is no evidence suggesting a direct survival benefit related to this reduction. Given this, the desire to scale back radiation therapy and its associated morbidities has led to recent trials evaluating de-escalation and even omission of radiation therapy for patients with DCIS.

TAILORING RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY

With growing randomized data demonstrating that hypofractionated radiation therapy offers similar results to standard radiation therapy for patients with invasive breast cancer [9▪▪], more patients are being treated with hypofractionated courses delivering lower overall doses over fewer fractions.

Recent data from the Danish British Cancer Group HYPO phase III randomized trial [10▪▪] demonstrates similar data for patients with DCIS. This study evaluated hypofractionated (40 Gy in 15 fractions) versus standard radiation (50 Gy in 25 fractions) for treatment of patients with early breast cancer and includes one of the largest cohorts of patients with DCIS randomized to hypofractionation. Of the 246 patients with DCIS, cosmetic outcome and patient satisfaction were similar to or better in the group who received the shorter hypofractionated course compared with standard therapy. The local recurrence rate was 7.7% at 9 years and did not differ between the hypofractionated versus standard radiotherapy groups.

These newer data suggest that standard radiotherapy may be over-treatment for patients with DCIS, and that lower doses over shorter time periods may be appropriate.

OMISSION OF RADIOTHERAPY AFTER BREAST-CONSERVING SURGERY FOR DUCTAL CARCINOMA *IN SITU*

With data emerging that support omission of radiation therapy for select patients with invasive breast cancer, similar trials have been conducted evaluating omission of radiation therapy for patients with DCIS, but results are less promising.

The ECOG-ACRIN E5194 study was a single-arm prospective trial evaluating omission of radiation therapy in women considered to have 'low-risk' DCIS [11]. Low risk was defined in this study as low/intermediate grade DCIS of 2.5 cm or less, or high-grade DCIS of 1 cm or less. All patients underwent excision with more than 3 mm margins and did not receive adjuvant radiotherapy. At a median follow-up of 12.3 years, 12-year cumulative IBTR

was 14.4% for those with low/intermediate grade and 24.6% for those with high-grade DCIS. Neither group (defined clinically as low risk) demonstrated a low risk of recurrence (i.e., <10%), but the risk of recurrence did differ significantly by grade.

The Radiation Therapy Oncology Group 9804 study compared radiotherapy with observation after lumpectomy for patients with DCIS [12]. Patients with mammographically detected, low/intermediate grade DCIS with lesions less than 2.5 cm who underwent BCT with at least 3 mm margins were eligible. Patients were randomized to WBRT versus observation. At first analysis at 7.2-year follow-up, the rate of local failure was 6.7% in the observation group versus 0.9% in the radiation group ($P < 0.001$).

These data suggest that clinicopathologic factors alone do not identify patients at low enough risk who would be recommended for omission of radiation therapy after surgery. Arguably, the definition of low recurrence risk is subjective, and the relative low rates of IBTR in these studies may be acceptable to some patients to consider omission of radiation therapy.

STRATIFYING PATIENT RISK

The ability to accurately identify patients at risk for invasive disease would better enable a more tailored approach to treatment of patients with DCIS.

Certain clinical and pathologic features have been associated with higher risks of recurrence, including young age at diagnosis (<50 years), high nuclear grade, presence of comedo necrosis, and positive/unknown margins.

Beyond clinicopathologic data, other tools are being developed to aid in risk stratification. The Oncotype DCIS Score is a 12-gene assay (seven cancer-related and five reference genes) that provides an estimated 10-year risk of IBTR after excision for DCIS and has been validated in two prospective cohort studies (ECOG-ACRIN E5194 and Ontario DCIS). However, in these studies, patients with a low score still had recurrence risk exceeding 10%, which is generally the recognized threshold for recommending radiation. Rakovitch *et al.* [13] was able to provide a more refined estimate of recurrence risk by combining Oncotype DCIS Score with patient age and tumor size, which better stratified patients to a low-risk (≤8%) versus high-risk (>15%) group for breast cancer recurrence at 10 years.

More recently, a biologic signature was identified that not only assesses recurrence risk but also predicts radiotherapy benefit in patients with DCIS [14]. Unlike Oncotype DCIS, the DCISionRT is both prognostic and predictive of radiation therapy benefit. Patients with a Decision Score of 3 or less were noted to have a low risk of recurrence of invasive disease of 4% at 10 years without radiation and radiation did not decrease risk further. For patients identified as high risk, IBTR reached 23% in 10 years, with a reduction to 11% with radiation. Radiotherapy reduced the risk of invasive disease by 6%.

The DCISionRT signature was independently validated on an external dataset, which corroborated the results. Patients classified as low risk (Decision Score ≤3) had a 10-year risk of invasive breast cancer of 5% without radiation therapy and 3% with radiation therapy. Patients with elevated risk (Decision Score >3) who did not receive radiation therapy had a 21% risk of in breast invasive cancer, while those receiving radiation therapy had a 6% risk [15▪].

The PREDICT study, a prospective, multiinstitutional, observational registry in which patients underwent DCISionRT testing, evaluated the impact of this testing on clinicians' recommendations for radiation therapy [16▪]. The results demonstrated that utilization of the DCISionRT test to stratify individual risk led to a significant overall change in radiation therapy recommendations. Among the 63% of patients with a low-risk score, recommendations for radiation therapy decreased by 45%; among patients with a high-risk score, recommendations increased by 21%. On logistic regression, the Decision Score was the greatest factor impacting decision to receive or omit radiation therapy (OR 43.4) over standard clinicopathologic factors.

These studies suggest that patients and physicians are eager for more objective data to predict risk and treatment benefit for patients with DCIS. Like the Oncotype DX score for invasive cancer, molecular tests may become more commonplace in the treatment algorithm for DCIS.

The use of artificial intelligence and machine-learning to analyze the vast amounts of molecular and histopathologic data available may also find a place in risk stratification of patients with DCIS.

Using machine-learning to digitally analyze fully annotated slides, a recurrence classifier based on eight unique histopathologic features was developed [17]. This signature outperformed standard clinicopathologic features in predicting patients at low and high risk for cancer recurrence.

OMISSION OF SURGERY FOR PATIENTS WITH LOW-RISK DUCTAL CARCINOMA *IN SITU*

Ongoing research is also focused on assessing whether a group of patients exists who is at low enough risk that active surveillance rather than

treatment would be appropriate. Four surveillance clinical trials for low-risk DCIS were initiated in the United Kingdom (LORIS), Europe (LORD), United States (COMET), and Japan (LORETTA) to assess active monitoring as an alternative to standard therapy [18]. The COMET trial is currently randomizing patients to active surveillance, consisting of monitoring with or without endocrine therapy, versus standard therapy. On the contrary, due to low accrual, the LORIS and LORD trials are continuing as registry trials. For the COMET trial, DCIS must be low to intermediate grade, and positive for both estrogen and progesterone receptor expression. Patients with comedo necrosis or who have undergone surgical excision but with positive margins are allowed. Patients with high-grade DCIS, however, are excluded from all monitoring trials.

Based on the considerable variability that exists among pathologists, the use of grade as a primary inclusion criteria for these monitoring trials may inadvertently lead to undertreatment of some patients misclassified as low/intermediate grade. Interrater variability among 38 pathologists of variable expertise demonstrated a poor, 69% agreement among raters for low/intermediate versus high-grade disease [19▪].

Methods to help standardize grading are necessary and are being actively pursued [20▪].

UPSTAGE RATES OF DUCTAL CARCINOMA *IN SITU*

In addition, when enrolling patients in observation trials for DCIS, the upstage rate to invasive cancer must be considered. A meta-analysis of over 52 studies demonstrated an overall upstage rate of DCIS to invasive cancer of 25.9% [21]. More recent data of 606 DCIS patients demonstrated a lower rate of upstage of 15.1% to invasive cancer and 14.6% to higher grade DCIS [22]. In this study, 65.1% of patients were diagnosed with DCIS using a 9G vacuum-assisted biopsy device compared with a 14G core biopsy device.

In the subset of patients who met inclusion criteria for the COMET and LORIS trials, upstage rates to invasive cancer ranged from 6 to 22% and 7 to 24%, respectively [23,24,25▪,26]. For patients who met eligibility criteria for the LORD trial, upstage rates of 5–10% were noted [23,25▪].

Clearly, this associated upstage rate raises the concern that patients randomized to active surveillance may have an invasive cancer left undiagnosed and untreated. Radiologists perform only slightly better than chance when predicting upstaging to invasive cancer by imaging criteria [27]. Results are improved when a two-stage approach is utilized in which radiologists review cases collectively in a focus group to develop consensus criteria to predict upstaging, and then proceed with independent review [28]. This suggests that radiologists can possibly be trained to improve predictive performance, which may help when selecting patients for consideration of surveillance trials.

ENDOCRINE THERAPY FOR RISK REDUCTION

Active surveillance can include the use of endocrine therapy. The primary role of endocrine therapy in DCIS is to reduce the risk of invasive breast cancer in the ipsilateral and/or contralateral breast. Current guidelines support the use of endocrine therapy for estrogen positive DCIS.

Despite evidence-based recommendations, less than half of women with DCIS take tamoxifen for risk reduction secondary to side effects and risk/benefit analysis [29]. As with surgery and radiation, efforts to de-escalate endocrine therapy are also being pursued. The Tam01 study, which randomized patients to 5 mg of tamoxifen daily for 3 years versus placebo, demonstrated a 50% reduction in ipsilateral breast cancer recurrence and 75% reduction in contralateral breast cancer development in women who received the low-dose therapy [30]. Hot flashes were only mildly increased in the treatment arm. Serious side effects did not differ between groups, and compliance to therapy was similar.

Low-dose tamoxifen may be an effective risk-reduction strategy with good tolerability for patients with DCIS, but data are still preliminary.

HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-DIRECTED THERAPY

NSABP B-43 is the first prospective, randomized phase III multiinstitutional clinical trial targeting high-risk, Human Epidermal Growth Factor Receptor 2 (HER2) - positive DCIS [31▪▪]. It compared WBRT alone or given concurrently with trastuzumab in women with HER2-positive DCIS treated by lumpectomy. This was a negative study in that the addition of trastuzumab to radiation therapy did not reach the prespecified reduction in IBTR of 36% although a modest reduction of 19% was noted.

Given that 35–50% of DCIS overexpress HER2 [32,33], the role of anti-Her directed therapy for DCIS should be pursued.

VACCINES

Vaccines in cancer have three potential uses: active cancer treatment, adjuvant therapy to prevent

cancer recurrence, and cancer prevention. There are more than 50 active clinical trials for vaccines in breast cancer, but their effectiveness is still unknown as the studies are in the earliest stages.

A phase II trial, the VADIS interventional trial, is evaluating the effect of vaccine therapy on the generation of an antitumor T-cell immune response in patients with DCIS. Vaccine toxicity and histologic response in the tumor will also be assessed [34].

CONCLUSION

Patients with DCIS have excellent breast cancer-specific survival, irrespective of their choice for therapy. As such, the pendulum for treatment appears to be swinging from standard therapy for all to de-escalation and even omission of therapy for some. As we examine the extremes of treatment, we should ask ourselves, 'What would Goldilocks do?', and look for that middle ground that will offer the appropriate level of treatment for each patient with DCIS.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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