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Management of Ductal Carcinoma In Situ of the Breast
A Review

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IMPORTANCE Ductal carcinoma in situ (DCIS) of the breast represents a disease process that continues to increase in incidence with treatment paradigms that continue to evolve. Greater access to long-term data from large observational studies addressing the natural history of the disease has contributed to changes in treatment paradigms and put into question traditional management strategies.

OBSERVATIONS While recent analyses have suggested that a more conservative approach to the management of DCIS without surgical intervention or radiation therapy may be advisable based on breast cancer mortality data, there is a lack of level 1 or prospective evidence to support the widespread adoption of these approaches. Currently, surgery remains the standard of care for the initial treatment of DCIS. Adjuvant radiation therapy (RT) has consistently demonstrated a reduction in the risk of local recurrence following breast-conserving surgery (BCS), even in "low-risk" populations of patients. Invasive recurrences following BCS are associated with increases in breast cancer mortality. Questions that remain to be answered include (1) what constitutes an acceptable risk of local recurrence, (2) what are the costs associated with managing local recurrences compared with RT given initially after BCS (particularly in light of data supporting shorter courses of RT), and (3) what are the benefits of endocrine therapy on local recurrence, and do they justify the additional toxic effects and potential noncompliance with their long-term administration?

CONCLUSIONS AND RELEVANCE Surgery and RT remain standard of care treatment options in the management of DCIS. Future studies are required to identify cohorts of patients in which RT can be safely omitted as well as to evaluate whether short-course RT alone may represent a better option than endocrine therapy with respect to compliance, toxic effects, cost and local control following BCS.

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The increased use of screening mammography over the past several decades has resulted in a dramatic rise in the diagnosis of ductal carcinoma in situ (DCIS) of the breast.[1] Traditionally, DCIS has been managed similarly to early-stage breast cancer with respect to local therapy with breast conservation and mastectomy as treatment options.[2-4] However, over the past 2 decades, questions have emerged as to whether current treatment paradigms for DCIS may represent overtreatment.[5,6] Narod et al[5] recently presented an observational study of more than 100 000 women diagnosed with DCIS, finding the 20-year rate of breast cancer mortality to be 3.3%. These rates of breast cancer mortality have led some to suggest a more conservative approach in many DCIS cases, including observation or endocrine therapy alone.[6,7] Despite the obvious appeal of these strategies, it is critical that clinicians remain keenly aware of the current state of the data regarding DCIS treatment and which therapies have been found to have a significant impact on clinically relevant outcomes. Therefore, the purpose of this review is to summarize the data regarding standard of care treatment options for DCIS in the modern era to provide a more realistic perspective as to the appropriateness of more conservative strategies for selected low-risk patients with DCIS.

Discussion

Surgical Techniques and Their Impact on Radiotherapy

Recent surgical advances in the treatment of DCIS include the incorporation oncoplastic procedures that include several techniques (tissue rearrangement, mastopexy, reduction mammoplasty, symmetry procedures). The specific technique used is based on several factors, including the patient's breast size/volume, tumor location, and lumpectomy cavity size.[8,9] Data on radiotherapy outcomes in patients undergoing oncoplastic techniques are limited, as are comparisons of toxic effects with and without their use. However, a study[10] from Turkey did find 12% and 15% rates of acute and chronic complications, respectively, with oncoplastic

Table 1. Randomized Clinical Trials Evaluating Radiotherapy Following Breast-Conserving Surgery

Trial	Patients	Years Treated	Follow-up, mo	Local Recurrence Rate (y), %
NSABP B17[18]	818	1985-1990	206	35 vs 20 (15)
EORTC 10853[19]	1010	1986-1996	188	31 vs 18 (15)
Swedish DCIS[17]	1046	1987-1999	204	32 vs 20 (20)
UKCCR[16]	1701	1990-1998	151	19 vs 7 (12)
RTOG 9804[26]	636	1998-2006	84	7 vs 1 (7)
Meta-analysis[20]	3729	NA	NA	28 vs 13 (1)

Abbreviation: NA, not applicable.

Table 2. Modern Trials Evaluating Breast-Conserving Surgery Alone

Trial	Patients, No.	Study Type	Years Treated	Follow-up, mo	Local Recurrence Rate (y), %
Dana Farber[24]	158	Prospective	1995-2002	132	16 (10)
ECOG E-5194[25]	670	Prospective	1997-2002	147	14/25 (12)[a]
RTOG 9804[26]	636	Randomized	1998-2006	84	7 vs 1 (7)

[a] Subset with multigene testing 11/27/26 (10) for low/intermediate/high score.

reduction mammoplasty, while a second series[11] from the University of California, San Francisco, found a 19% rate of at least 1 breast complication. While oncoplastic techniques are particularly promising in their potential to reduce acute and chronic radiation skin complications associated with larger-breasted patients, the potential benefits of breast reduction and reduced complications with radiotherapy need to be weighed against the additional procedures, which can also increase toxicity. As the use of oncoplastic techniques continue to expand, a challenge for radiation oncologists is identifying the lumpectomy cavity or tissue at risk for a tumor bed boost. Although surgical clips have traditionally been used, with tissue rearrangement it becomes unclear if they remain surrogates for the "at risk" marginal tissue surrounding the lumpectomy cavity. This is of clinical importance because a tumor bed boost has been shown to reduce rates of local recurrence with invasive cancers as well as with DCIS.[12,13] Furthermore, the absolute benefit of a tumor bed boost on local control is greatest among younger women. Techniques to appropriately boost the cavity should be identified to maximize tumor control.[12]

Radiation Therapy

To understand the concerns regarding deintensification, it is important to first review the evolution of treatment for DCIS. Initially, breast-conserving therapy (based on data from invasive cancers), was felt to be an appropriate treatment approach for patients with DCIS using breast-conserving surgery (BCS) followed by adjuvant whole-breast irradiation (WBI).[14,15] In the 1980s and 1990s, 4 randomized clinical trials (RCTs) (NSABP B17, EORTC 10853, SweDCIS, and UKCCR) were performed to evaluate whether WBI was needed following BCS in women with DCIS (**Table 1**).[16-19] The NSABP B17, EORTC 10853, and SweDCIS trials randomized women following BCS to adjuvant WBI (50 Gy) or no further treatment and found a roughly 35% to 45% reduction in local recurrence with WBI (NSABP B17: 15 years, 35% vs 20%; EORTC 10853: 15 years, 31% vs 18%; SweDCIS: 20 years, 32% vs 20%). The UKCCR trial was a 4-arm study (observation, tamoxifen, WBI, WBI plus tamoxifen following breast-conserving surgery) with WBI found to reduce local recurrences independent of endocrine therapy (19% vs 7%).[16] Furthermore, the EBCTG meta-analysis of more than 3700 patients found that adjuvant WBI following BCS reduced local recurrences 15% (28% vs 13%) for all patients. The analysis found that low-risk patients (small tumor, low grade, and negative margins) still benefited from radiation therapy with respect to rates of local recurrence(30% vs 12%).[20] Similarly, a Surveillance, Epidemiology, and End Results (SEER) analysis of over 32 000 patients with DCIS (1988-2007) found a reduction in breast cancer mortality with the addition of RT to BCS, particularly for those patients with high-grade disease, young age, and large tumor size.[21] It should be noted that most studies documented all ipsilateral breast recurrences rather than local recurrences, making it difficult to determine a true recurrence of the index lesion vs a new cancer. While these trials are criticized for a failure to use modern techniques, recent studies[22,23] using contemporary approaches have demonstrated low rates of local recurrence in patients with DCIS undergoing radiotherapy. However, because invasive recurrences can represent greater than 50% of all local recurrences, concerns exist since these occurrences are associated with higher rates of mortality.[5,18]

While the RCTs discussed herein made adjuvant radiotherapy standard following BCS, more recent studies have attempted to determine if low-risk patients (as defined by pathologic criteria) derived a similar benefit (**Table 2**). A prospective study from the Dana Farber Cancer Institute enrolled 158 patients (with low- to intermediate-grade DCIS; ≤2.5 cm; margins ≥1 cm) to excision alone and found a 10-year local recurrence rate of 16% (1.9%/year). However, a major limitation of this study is that patients did not receive endocrine therapy.[24] Similarly, the ECOG-ACRIN E5194 prospective study enrolled 561 low-risk patients (low- to intermediate-grade DCIS; ≤2.5 cm; margins ≥3 mm) and 104 high-risk patients (high-grade DCIS; ≤1 cm; margins ≥3 mm) to observation alone following excision (30% received tamoxifen, not randomly assigned). At 12 years, the rate of ipsilateral breast recurrence was 14.4% and 24.6% for the low-risk and high-risk cohorts, respectively.[25] Taken together, these studies demonstrate a "substantial and ongoing risk of local recurrence" with excision alone.[24,25] More recently, the RTOG 9804 trial randomized patients with low-risk DCIS (low- to intermediate-grade; ≤2.5 cm; margins ≥3 mm) to RT or observation following BCS with 62% of patients receiving tamoxifen. With 7 years of follow-up (closed early owing to slow accrual; 636 accrued), RT reduced the rate of local recurrence (6.7% vs 0.9%) with low rates of complications noted.[26]

Because clinical and pathologic characteristics have failed to identify a low-risk cohort of patients who do not benefit from adjuvant radiotherapy with respect to local control, studies are now being performed to determine if multigene expression can be used to identify such cohorts. Solin et al[27] evaluated a subset of the ECOG trial using such an approach but found the low-risk DCIS cohort still had a 10-year local recurrence risk of 11% (with rates of 27% and 26% for the intermediate- and high-risk groups). A second analysis from Rakovitch et al[28] using a multigene expression assay did demonstrate the ability to stratify by local recurrence (local recurrence: 12.7%, low risk; 22%, intermediate risk; 28%, high risk); however, further study is required prior to widespread utilization of such approaches because the low-risk groups identified with such assays still have local recurrence rates exceeding 10% with long-term follow-up as well as the cost associated.

Owing to the inability to identify low-risk subsets of patients who do not benefit from adjuvant WBI with respect to local control, alternative strategies to standard WBI have altered the treatment landscape, allowing the ability to maximize local control while limiting the duration of adjuvant RT to 1 to 3 weeks. Accelerated, hypofractionated whole-breast irradiation (AWBI) allows for the completion of radiotherapy in 3 weeks with multiple RCTs demonstrating no difference in local recurrence compared with standard WBI.[29,30] The Ontario Clinical Oncology Group trial[29] randomized 1234 women with early-stage invasive breast cancers (T1-2N0 with negative margins) to standard WBI or AWBI; at 10 years, no difference in local recurrence was noted (6.7% WBI vs 6.2% AWBI) with no difference in toxicity or cosmetic outcomes. Similarly, the MRC START A (WBI 50 Gy in 25 fractions vs AWBI 39 or 41.6 Gy in 13 fractions over 5 weeks) and START B (WBI 50 Gy vs AWBI 40 Gy in 15 fractions over 3 weeks) trials evaluated AWBI with both finding no difference in rates of local control (START A: 7.4% 50 Gy vs 6.3% 41.6 Gy vs 8.8% 39 Gy; START B: 5.5% 50 Gy vs 4.3% 40 Gy) and with both demonstrating reductions in breast edema, telangiectasias, and breast shrinkage using AWBI.[30] While these studies had limited numbers of patients with DCIS, recent reports have demonstrated the safety and efficacy of AWBI in patients with DCIS. Lalani et al[31] evaluated 1609 patients with DCIS treated in Ontario between 1994 and 2003 and compared WBI with AWBI, finding improved local control with AWBI (89% vs 86%; $P = .03$). As such, AWBI represents an excellent alternative to standard WBI if patients meet appropriate technical and treatment factors based on evidence based guidelines (age >50 years, no chemotherapy, maximum whole-breast dose <107% of prescription).[32]

Another alternative to standard WBI and AWBI is a partial breast approach, which targets the lumpectomy cavity and a surrounding margin of tissue.[33] Accelerated partial breast irradiation (APBI) offers patients multiple options as it can be delivered via brachytherapy (interstitial, or applicator based) or external beam RT (3-dimensional conformal radiation therapy, intensity-modulated radiation therapy) approaches. Four contemporary RCTs to date have demonstrated no difference in local recurrence compared with standard WBI, while the IMPORT LOW trial has been presented and demonstrated no difference in outcomes with APBI compared with AWBI.[34-37] Recently, results of the GEC-ESTRO trial, which randomized women with early-stage breast cancer to WBI or APBI delivered via interstitial brachytherapy, were published. At 5 years, no difference in rates of local recurrence was noted (0.9% WBI vs 1.4% APBI) with trends for a reduction in late grade 2 to 3 skin toxic effects with APBI.[34] Similarly, Livi et al[35] presented 5-year outcomes from an RCT comparing WBI and APBI delivered with external beam radiotherapy (IMRT). No difference in local recurrence was noted (1.5% for both arms) with APBI associated with improved acute and late toxicity outcomes as well as cosmesis. While these RCTs had limited numbers of patients with DCIS, series evaluating outcomes in patients with DCIS have similarly demonstrated low rates of local recurrence[38-41]; the largest published series from Vicini and colleagues[41] evaluated 300 patients treated with various APBI techniques and found a 2.6% rate of local recurrence at 5 years. Recently, the American Brachytherapy Society consensus statement for APBI was released and included DCIS, based on more recent data, supporting this as a standard approach in appropriately selected women (age ≥50 years, ≤3 cm, negative margins, no lymphovascular space invasive, node negative).[42] APBI can be used based on these evidence-based guidelines or the inclusion criteria from RCTs.[34-37,42] Intraoperative radiation therapy (IORT) is considered a partial breast technique but should not be used off-protocol at this time in light of higher rates of local recurrence reported in 2 randomized studies of patients with early-stage breast cancer (the ELIOT trial: 4.4% IORT vs 0.4% WBI, and the TARGIT trial: 3.3% IORT vs 1.3% WBI).[43,44] With respect to DCIS, a small, series of patients undergoing IORT[45] demonstrated a local recurrence rate of 5.7% with a follow up of 36 months, higher than seen with WBI, AWBI, or APBI.

Endocrine Therapy

Endocrine therapy should be considered as a part of adjuvant therapy for patients with DCIS. Data supporting its efficacy come from the NSABP B24 trial, which randomized patients to tamoxifen or placebo following BCT. Tamoxifen use was associated with a 32% reduction in invasive ipsilateral recurrences (6.6% vs 9.0%) and a 32% reduction in contralateral breast cancers (4.9% vs 8.1%) as well as a nonsignificant reduction in DCIS ipsilateral recurrences (6.7% vs 7.6%). No differences in survival were noted. Together, RT and tamoxifen reduced invasive ipsilateral breast tumor recurrences by 70% compared with lumpectomy alone (NSABP B24, 16.6%, vs NSABP B17, 35%).[36] It is important to note that when evaluating the benefit of tamoxifen, analyses have demonstrated that the majority of reduction in recurrences was observed in patients with positive margins, whereas limited benefit was derived from tamoxifen for patients with negative surgical margins.[18] The UKCCR trial, however, did find a reduction in DCIS recurrences with tamoxifen with no reduction in invasive recurrences noted, different than the NSABP B24 findings.[16] Recent publication of the NSABP B35 trial, which randomized postmenopausal women with DCIS to tamoxifen or anastrazole, found that anastrazole was associated with an improvement in breast cancer–free interval (93.5% vs 89.2%) at 10 years with the benefit from anastrazole primarily noted in women younger than 60 years.[46] This supports the use of aromatase inhibitors in postmenopausal women with DCIS undergoing BCT. However, it should be noted that recent data demonstrate that a minority of patients (36.5% of all patients, 46.4% of estrogen receptor–positive patients) with DCIS receive endocrine therapy and concerns regarding noncompliance exist for those prescribed endocrine treatment.[47,48] As such, endocrine therapy remains an option for patients, but one which should be guided by an informed discussion between the patient and the clinicians involved.

Table 3. Observational DCIS Studies

Source	Patients	Data Source	Years Treated	Follow-up, mo	Local Recurrence Rate, %
Narod et al[5]	108 196	SEER	1988-2011	90	3.3% Increased breast cancer mortality with young age (<35 y) and black patients; ipsilateral invasive recurrence associated with higher risk of breast cancer mortality
Duffy et al[51]	5 243 658	NHS	2003-2007	36	For every 3 screen-detected DCIS cases, 1 fewer invasive cancer in the next 3 years

Abbreviations: DCIS, ductal carcinoma in situ; NHS, National Health Service (United Kingdom); SEER, Surveillance, Epidemiology, and End Results.

Future Directions

The data regarding radiotherapy for DCIS are consistent in demonstrating a reduction in the risk of local recurrence. However, one of the important questions remaining to be answered is "What is an acceptable increase in local recurrence risk when treatment de-escalation is attempted?" To answer this question, several variables must be taken into consideration, with the most important being patient choice. To provide a patient the ability to make informed decisions on this issue, quantifying risk is critical. Data from the Dana Farber and ECOG trials provide 2 salient pieces of information: (1) the risk of recurrence at 10 to 12 years without radiation therapy is 14% to 16% for low-risk patients and 25% for high-risk patients, and (2) the risk of recurrence in both of these trials has not yet plateaued.[24,25] Further additional factors to be considered include (1) the cost of upfront radiotherapy vs the costs of managing recurrences (including the need for systemic therapy with invasive recurrences) and (2) the adverse effects of upfront radiotherapy vs potential impairment in quality of life with higher rates of recurrences and adverse effects associated with salvage treatment, and (3) the potential for an increase in breast cancer mortality and overall mortality for those that develop invasive recurrences (EORTC 10853 overall survival hazard ratio, 5.17; breast cancer–specific survival hazard ratio, 17.66 for those patients developing an invasive local recurrence compared with no recurrence).[19] An additional factor to consider is overall treatment costs. Using shorter courses of radiation, the costs of upfront radiotherapy have been reduced while the treatment of local recurrences often involve surgery with the potential for adjuvant radiation and systemic therapy. While current and future studies are evaluating patient and tumor characteristics as well as tumor genetics to identify low-risk cohorts of patients, until a consistent and reproducible "low-risk" group is defined, it is unlikely clarity will occur as to which patients should receive adjuvant treatment following surgery and which can be observed.

Another potential direction in the future management of DCIS is focused on choosing a different adjuvant treatment to possibly eliminate. As discussed herein, studies attempting to deintensify treatment for patients with DCIS have evaluated the omission of RT with endocrine therapy alone following BCS. However, this was based on traditional WBI, which had a longer duration of treatment (5.0-6.5 weeks) and higher rates of toxic effects. New radiation therapy techniques and schedules allow for a reduction treatment duration and acute and chronic toxic effects.[29,30,34-37,49] A new question to be asked is whether radiation therapy alone following surgery is a more appropriate option than endocrine therapy (noncompliance, toxicity, 5 years of treatment), in light of recent data suggesting limited long-term benefit of tamoxifen in preventing invasive local recurrences and questions on whether the benefit of endocrine therapy on local control is limited to patients with positive margins, understanding the potential for an increased risk of contralateral breast cancers with omitting endocrine therapy.[4,18,47,48,50]

Recently, there has been suggestion of a further deintensification of treatment, which has gained publicity and led some to question current treatment approaches (**Table 3**). This new approach has consisted of biopsying and confirming the presence of DCIS with no further upfront treatment other than endocrine therapy (in some cases) with subsequent clinical and mammographic surveillance.[5-7] These suggestions are based on observational data that have demonstrated a low risk of mortality with DCIS, regardless of its management.[5] While concepts such as this are hypothesis generating and can lead to novel studies (eg, CALGB 40903), they neither represent level 1 evidence to support deintensification nor do they support off-protocol use of such approaches. This is particularly true based on recent observational data. In a large study of more than 5 million patients, an association was demonstrated between DCIS detected through screening and a decrease in the subsequent development of invasive interval cancers (reduction of 1 invasive cancer per 1.5-3.0 cases of DCIS detected).[51] In light of the contradictory findings of these observational studies and the concerns with their lack of reproducibility, clinicians must continue to use prospective level 1 evidence to guide treatment decisions for women with DCIS.[52] At this time, the standard of care following BCS remains radiotherapy as indicated and consideration for endocrine therapy.

Conclusions

Treatment paradigms for DCIS continue to evolve. However, active treatment currently remains the standard of care. Treatment options range from mastectomy to breast conservation (including radiotherapy) with or without long-term endocrine therapy following treatment. While the value of RT following lumpectomy has been questioned, the data continue to support its use to reduce the risk of local recurrences. Unfortunately, no cohort of patients has yet to be identified (based on patient, pathologic, or treatment criteria and/or tumor genetics) that does not benefit from adjuvant radiation to some extent with respect to local control. Future studies will continue to explore if such subsets can be identified routinely. In addition, analyses directly comparing the increased costs associated with managing local recurrences (in addition to their impact on quality of life and toxicity) vs the upfront costs of adjuvant RT need to be performed to truly evaluate the overall "value" of these differing treatment strategies.

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