Advances in Surgery 53 (2019) 21–35
ADVANCES IN SURGERY

Ductal Carcinoma In Situ of the Breast

Controversies and Current Management

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Keywords

• DCIS • Local recurrence • Margin width • Surgery • Radiation
• Endocrine therapy

Key points

- Radiation therapy (RT) reduces risk of local recurrence after breast-conserving surgery (BCS) by half, but may be associated with serious side effects.
- Endocrine therapy reduces risk of local recurrence after BCS and RT by 30% in women with estrogen receptor-positive ductal carcinoma in situ (DCIS), but can be associated with side effects that reduce compliance.
- In patients receiving RT, a margin width of 2 mm reduces risk of local recurrence compared with a narrower negative margin.
- In select low-risk subsets of DCIS (ie, low-to-intermediate grade, small tumor size <2.5 cm, and age >50 years), absolute risk of local recurrence following BCS may be sufficiently low that omission of RT may be appropriate.
- Nonoperative management of highly select patients with low-risk DCIS should only be performed in a clinical trial.

INTRODUCTION

Ductal carcinoma in situ (DCIS) is a noninvasive malignancy of the breast, and comprises nearly 20% of all newly diagnosed breast cancers [1]. The standard treatment of DCIS is primarily surgical and includes mastectomy for extensive or multicentric disease, and breast-conserving surgery (BCS) for localized

Disclosure Statement: Dr A.V. Barrio has received speaking honorarium from Roche. Dr K.J. Van Zee has nothing to disclose.

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https://doi.org/10.1016/j.yasu.2019.04.002

lesions. Although the risk of local recurrence (LR) following mastectomy is minimal, long-term LR rates following excision alone in the early randomized trials were 25% to 35%, with half of those recurrences being invasive [2–5].

Four prospective randomized trials begun between 1985 and 1990 have demonstrated a significant reduction in both invasive and DCIS recurrence with the addition of adjuvant radiation therapy (RT) following BCS, with no impact on survival [2–5]. Adjuvant endocrine therapy further reduces LR by approximately 30% in patients with estrogen receptor (ER)-positive DCIS, although the side-effect profile of these medications reduces uptake and compliance [2,4,6–8].

Among select women with low-risk DCIS treated with BCS alone, more recent prospective trials have demonstrated lower rates of LR than seen in the original randomized trials [9–11]. These observed lower rates of LR, coupled with the excellent survival after surgical treatment of DCIS [12], have raised concerns regarding potential overtreatment of patients, particularly with respect to the appropriate use of adjuvant RT and endocrine therapy, and their associated morbidity.

This controversy has led to interest in identifying a subset of "low-risk" patients who could be managed without any surgical excision. Although there is no evidence that omission of surgery is safe in patients with DCIS, trials of observation in very select patients with DCIS are ongoing in the United States and Europe [13–15], leaving many to incorrectly extrapolate that observation is appropriate in certain DCIS subsets outside of a clinical trial.

SIGNIFICANCE

Standard treatment of ductal carcinoma in situ

As a noninvasive cancer, treatment of DCIS is focused on complete surgical removal of disease in the breast with the goal of preventing LR, particularly invasive recurrence. To that end, appropriate treatment options include mastectomy alone or BCS with or without adjuvant RT and/or endocrine therapy. Each of these options results in a low mortality rate, although LR rates vary across treatments [2–5,12,16].

Mastectomy

Mastectomy was once the gold standard for all patients with any type of breast cancer, including DCIS, regardless of disease extent. Following publication of the randomized trials demonstrating equivalent survival between mastectomy and BCS in women with invasive disease [17–22], clinicians surmised that BCS would similarly be acceptable in women with localized DCIS. Currently, mastectomy is considered necessary only for women with more extensive or multicentric DCIS. A meta-analysis of 8 studies that reported outcomes for women with DCIS treated with mastectomy found a 2.6% (95% CI, 0.8%–4.5%) 10-year LR rate [23].

Breast-conserving surgery with or without adjuvant radiation therapy

Even in the absence of randomized data comparing recurrence and overall survival between mastectomy and BCS in women with DCIS, BCS became the

preferred approach for patients with localized DCIS, based on inferences from the randomized trials in invasive cancer that showed equivalent long-term survival [17–22].

Data from 4 prospective randomized trials comparing adjuvant RT to no RT following BCS demonstrated an approximately 50% LR reduction with the addition of RT (Table 1) [2–5]. An individual patient-level meta-analysis of the 4 randomized trials performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which included 3729 women with DCIS, demonstrated an absolute 15.2% 10-year reduction in LR risk with RT use (28.1% without RT, 12.9% with RT, $P<.00001$) [16]. The benefit of RT was observed in all patient subsets regardless of patient age, margin status, focality, grade, or tumor size [16]. Importantly, in the meta-analysis and the individual randomized trials [2–5], RT use also reduced the invasive recurrence risk by approximately half (for example, 15-year invasive LR rates from National Surgical Adjuvant Breast and Bowel Project [NSABP] B-17: 19.4% without RT, 8.9% with RT) [2–5,16].

Despite the LR reduction observed with RT, there was no effect on 10-year breast cancer mortality (3.7% without RT, 4.1% with RT, $P = $ NS) or all-cause mortality (8.2% without RT, 8.4% with RT, $P = $ NS) (Table 2) [16]. Notably, RT is associated with a higher cardiovascular disease rate and rare malignancies such as radiation-associated angiosarcoma [24,25]. Without a benefit in survival observed with RT among patients with DCIS, adjuvant RT use

Table 1
Ipsilateral local recurrence from the randomized trials comparing adjuvant radiotherapy to no radiotherapy following breast-conserving surgery for ductal carcinoma in situ

				Local recurrence		
Study	Study dates	N	Follow-up (y)	No RT (%)	RT (%)	Relative risk reduction (%)
NSABP B-17 [4]	1985–1990	813	15	35	18	50
EORTC 10853 [3]	1986–1996	1010	15	31	18	48
SweDCIS [5]	1987–1999	1046	20	32	20	37.5
UK/ANZ DCIS [2]	1990–1998	475	12.7 median	25	9	69
EBCTCG meta-analysis [16]	1985–1999	3729	10	28.1	12.9	54

Note: The NSABP and EORTC data are 15-year local recurrence rates, the SweDCIS data are 20-year local recurrence rates, and the UK/ANZ data are crude rates for those not receiving tamoxifen, and randomized to no radiotherapy versus radiotherapy. EBCTCG data are 10-year rates from a patient-level meta-analysis of the 4 randomized trials listed above it in the table.

Abbreviations: DCIS, ductal carcinoma in situ; f/u, follow-up; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; EORTC, European Organisation for Research and Treatment of Cancer; NSABP, National Adjuvant Breast and Bowel Project; RT, radiation therapy; SweDCIS, Sweden Ductal Carcinoma In Situ; UK/ANZ; United Kingdom/Australia/New Zealand.

Data from Refs [2–5].

Table 2
Breast cancer mortality from the randomized trials comparing adjuvant radiotherapy to no radiotherapy following breast-conserving surgery for ductal carcinoma in situ

				Breast cancer mortality		Overall mortality	
Study	Study dates	N	Follow-up (y)	No RT (%)	RT (%)	No RT (%)	RT (%)
NSABP B-17 [4]	1985–1990	813	15	3.1	4.7	15.7	17.1
EORTC 10853 [3]	1986–1996	1010	15	5	4	10	12
SweDCIS [5]	1987–1999	1046	20	4.2	4.1	27.0	22.8
UK/ANZ DCIS [2],[a]	1990–1998	811[a]	12.7 median	2.0	1.5	9.6	9.7
EBCTCG meta-analysis [16]	1985–1999	3729	10	3.7	4.1	8.2	8.4

Note: The NSABP and EORTC data are 15-year rates, the SweDCIS data are 20-year rates, and the UK/ANZ data are crude rates for those not receiving tamoxifen. EBCTCG data are 10-year rates from a patient-level meta-analysis of the 4 randomized trials listed above it in the table.

Abbreviations: DCIS, ductal carcinoma in situ; EBCTCG, Early Breast Cancer Trialists' Collaborative Group; EORTC, European Organisation for Research and Treatment of Cancer; NSABP, National Adjuvant Breast and Bowel Project; RT, radiation therapy; SweDCIS, Sweden Ductal Carcinoma In Situ; UK/ANZ; United Kingdom/Australia/New Zealand.

[a]Patients not receiving tamoxifen.

Data from Early Breast Cancer Trialists' Collaborative G, Correa C, McGale P, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010;2010(41):162–177.

should be selective, and reserved for those patients at higher risk for LR and thus likely to derive greater benefit from its use.

Adjuvant endocrine therapy following breast-conserving surgery

The use of tamoxifen following BCS in women with DCIS has been demonstrated in 2 large randomized trials to reduce LR with a relative risk reduction of approximately 25% (Table 3). Notably, in the UK/ANZ (United Kingdom/Australia/New Zealand) DCIS trial, the observed reduction in ipsilateral breast events with tamoxifen was limited to those patients *not* receiving RT (hazard ratio [HR] = 0.77), whereas in NSABP B-24, all women received RT, and they experienced a similar reduction in risk (HR = 0.68 for invasive LR; 0.84 for DCIS LR). In both trials, the addition of tamoxifen was also associated with a reduction in contralateral breast cancer (32% in NSABP B-24, 54% in UK/ANZ). As expected, the use of adjuvant tamoxifen was not associated with a reduction in breast cancer or overall mortality in either trial (Table 4) [2,4].

The hormone receptor status of patients enrolled in NSABP B-24 and the UK/ANZ trial was unknown, but retrospective analysis of 732 cases from B-24 confirmed that the benefit of tamoxifen was limited to ER-positive DCIS. In these patients, tamoxifen was associated with a 42% reduction in any breast event ($P = .0015$) and a 32% reduction in any ipsilateral breast cancer ($P = .07$) (see Table 3) [6].

Table 3
Review of the randomized trials comparing ipsilateral local recurrence after breast-conserving surgery with or without adjuvant tamoxifen

				Ipsilateral Local Recurrence		Risk Reduction	
Study	Study Dates	N	Follow-up (y)	No Tam (%)	Tam (%)	HR	*P* value
UK/ANZ DCIS [2],[a]	1990–1998	1576	10	19.6	15.7	0.78	.04
No RT[b]		1053	12.7 median	26.4	20.9	0.77	.04
RT[b]		523	12.7 median	8.8	7.4	0.93	.8
NSABP B-24 [4],[c]	1991–1994	1799	15	18.3	16.0	NR	NR
NSABP B-24 ER+ cases [6],[c]	1991–1994	732	14.5 median	17	14	0.68	.07

Abbreviations: f/u; follow-up; Tam, tamoxifen; HR, hazard ratio; RT, radiation therapy; UK/ANZ; United Kingdom/Australia/New Zealand; NSABP, National Adjuvant Breast and Bowel Project; NR, not reported.

[a]UK/ANZ patients randomized to tamoxifen or placebo include 1053 not receiving RT and 523 receiving RT. Reported percentages are 10-year estimates.

[b]Percentages reflect crude number of events/total number of patients randomized to tamoxifen or no tamoxifen, by receipt of RT, at a median follow-up of 12.7 years.

[c]In NSABP B-24, all patients received RT.

Data from Allred DC, Anderson SJ, Paik S, et al. Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: a study based on NSABP protocol B-24. J Clin Oncol 2012;30(12):1268–1273.

Anastrozole was compared with tamoxifen in postmenopausal women with hormone receptor-positive DCIS treated with BCS in NSABP B-35 and the International Breast Cancer Intervention Studies (IBIS)-II trials [7,8]. All 3104 women in B-35 and 71% of the 2980 women in IBIS-II received RT. In B-35, the 10-year breast cancer event rate was lower among women randomized to anastrozole compared with tamoxifen (6.9% [anastrozole] vs 10.9% [tamoxifen], HR = 0.73, $P = .02$) [8]. In IBIS-II, at a median follow-up of 7.2 years, anastrozole was demonstrated to be noninferior to tamoxifen with a similar breast cancer event rate in either group (5%) [7].

Notably, although adjuvant endocrine therapy does reduce the incidence of LR in women with DCIS treated with local excision, many patients experience side effects including a higher incidence of thromboembolic events and endometrial cancer with tamoxifen, and arthralgias, osteoporosis, and vaginal dryness with aromatase inhibitors [26]. The lack of survival benefit observed with endocrine therapy in patients with DCIS, combined with their side-effect profile, limits uptake of endocrine therapy, which is reported in only 20% to 48% of DCIS patients [27–29].

Factors associated with local recurrence

Although the randomized trials demonstrated that the risk of LR with excision alone for DCIS was substantial [16], more recent evidence suggests that risk of recurrence is influenced by several clinical and pathologic factors that may be used to estimate risk and make treatment decisions regarding adjuvant therapy.

Table 4
Randomized trials comparing breast cancer and overall mortality after breast-conserving surgery with or without adjuvant tamoxifen

				Breast cancer mortality		Overall mortality	
Study	Receipt of Radiation	N	Follow-up (y)	No Tamoxifen (%) n/N	Tamoxifen (%) n/N	No Tamoxifen (%) n/N	Tamoxifen (%) n/N
UK/ANZ DCIS [2]	No RT	1111	12.7 median	2.0 (11/544)	3.4 (19/567)	9.6 (52/544)	10 (58/567)
UK/ANZ DCIS [2]	RT	583	12.7 median	1.5 (4/267)	1.6 (5/316)	9.7 (26/267)	14 (43/316)
NSABP B-24 [4]	RT	1799	15	2.7[a]	2.3[a]	17.1[b]	14.3[b]

Note: UK/ANZ rates are crude rates. B-24 are 15-year rates.

Abbreviations: NSABP, National Adjuvant Breast and Bowel Project; RT, radiation therapy; UK/ANZ; United Kingdom/Australia/New Zealand.

[a]HR tamoxifen versus no tamoxifen for breast cancer mortality: 0.81 (95% CI, 0.43–1.50).

[b]HR tamoxifen versus no tamoxifen for overall mortality: 0.86 (95% CI, 0.66–1.11).

Data from Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol 2011;12(1):21–29; and Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 2011;103(6):478–488.

Age

Both retrospective [30,31] and randomized trials [2–5] have demonstrated young age to be associated with a higher LR risk among patients with DCIS treated with BCS. Cronin and colleagues [32] examined the relationship between age and LR among nearly 3000 women with DCIS treated with BCS at Memorial Sloan Kettering Cancer Center (MSK); 53% of women received RT. The 10-year rates of any LR were lower among women age $\geq$80 years (7.5%) compared with women age <40 (27.3%, $P<.0001$), and the effect of age persisted on multivariable analysis, even after adjusting for 8 clinicopathologic and treatment variables. Importantly, women age <40 years were at a significant risk of invasive recurrence, with a 10-year rate of 15.8% compared with 6.5% for those age $\geq$40. Although young women age <40 years with localized disease are still considered appropriate candidates for BCS, the higher LR risk should be discussed with young patients when considering appropriate surgical and adjuvant treatment options. Alternatively, the lower recurrence risk seen in older women suggests that many of them may be adequately treated with excision alone and may garner only a small absolute benefit to adjuvant therapy.

Volume of ductal carcinoma in situ

The EBCTCG meta-analysis failed to demonstrate a difference in 10-year LR rates between patients with small DCIS tumors (13.1%, 13.1–20 mm) versus larger tumors (13.0%, 20–50 mm) treated with BCS + RT [16]. However, more recent prospective trials [10] of DCIS have demonstrated increasing tumor size to be associated with a higher LR risk following BCS in the absence

of adjuvant RT. In the Eastern Cooperative Oncology Group-Radiation Therapy Oncology Group (ECOG-ACRIN) E5194 study, a prospective study of 665 patients with low-risk DCIS treated with excision alone, increasing tumor size was significantly associated with a higher LR risk (5 mm reference group, HR = 1.42 [6–10 mm], HR = 2.11 [>10 mm], $P = .03$) [10]. This lower rate of LR observed among patients with small-volume DCIS raises the question of whether excision alone may be sufficient in these patients. Muhsen and colleagues [33] examined LR risk among 290 patients with minimal volume DCIS, defined as DCIS diagnosed on the core biopsy with no residual disease identified at excision, using the contralateral breast as a control. Overall, 28% of patients received RT and, in this group, the 10-year LR risk was 6.5%, lower than the contralateral breast cancer risk. Contrastingly, among those who did not receive RT, the 10-year LR rate was 14.7% and higher than the contralateral breast cancer risk, highlighting that even patients with small-volume disease are not at negligible risk of local failure when treated with excision alone. Patients with small-volume disease should be considered for adjuvant therapy if other clinical and pathologic factors suggest high-risk disease.

Treatment period

LR rates in women with invasive breast cancer have declined over time, largely because of systemic therapy improvements [34–36]. Similar trends have been noted among women with DCIS treated with BCS, although the reason for this is multifactorial, as most women with DCIS do not receive systemic therapy. Subhedar and colleagues [37] examined temporal trends in recurrence rates among 2996 women treated with BCS at MSK over 3 decades. Between 1978 and 2010, a significant decrease in recurrence rates over time was observed ($P = .001$). Ten-year rates of recurrence significantly decreased from 20% in women treated from 1978 to 1998 to 14% in women treated from 1999 to 2010 ($P<.0001$). Even after controlling for multiple clinicopathologic variables, treatment period remained significant, with a lower recurrence risk in patients treated in the later time period (HR = 0.74, $P = .02$). The association of recurrence with treatment period was limited to those treated without RT (HR = 0.62, $P = .003$), suggesting factors other than improvements in radiation technique, including improved radiologic detection and pathologic assessments, may explain the decline [37].

Margin width

The randomized trials of RT demonstrated that positive margins are associated with a higher rate of LR in women with DCIS treated with BCS [2–5]. In NSABP B-24, a randomized trial of tamoxifen versus placebo in women with DCIS treated with BCS and RT, 25% of the 1799 women enrolled had positive margins and had a more than 2-fold increase in invasive recurrence compared with women with negative margins (HR = 2.61; 95% CI, 1.68–4.05; $P<.001$). In 3 of the 4 randomized trials, a negative margin was defined as no tumor on ink, and, therefore, these studies could not be used to determine the ideal negative margin width to minimize the risk of LR [2–5].

In 2016 the Society of Surgical Oncology, American Society for Radiation Oncology, and the American Society of Clinical Oncology published a consensus statement [38] on margins for women with DCIS treated with BCS and RT based on a study-level meta-analysis of nearly 8000 women for whom margin status was available [39]. A margin width of at least 2 mm was associated with a lower risk of LR compared with a narrower negative margin width (odds ratio [OR] = 0.51; 95% CI, 0.31–0.85, frequentist analysis). In addition, a more widely negative margin (>2 mm) did not further reduce the risk of LR (relative OR = 0.99; 95% CI, 0.61–1.64) [39]. Although a margin width of at least 2 mm is considered optimal, selective re-excision of a narrower margin (<2 mm) may be appropriate in certain cases in which the residual volume of disease in the breast is perceived to be minimal. In addition, if the original disease was associated with calcifications, a postexcision mammogram may be useful to identify the presence of residual calcifications, which would prompt a return trip to the operating room.

Women who underwent BCS without RT were not included in the meta-analysis due to the limited number of studies available. However, Van Zee and colleagues [40] examined 1374 women who were treated with BCS without RT and found that increasing negative margin width was associated with a lower risk of recurrence ($P<.0001$). Among those with a negative margin width of over 10 mm, or who underwent a re-excision with no residual DCIS found, 10-year LR rates were 16% compared with 41% with positive margins, and 27% with close (≤2 mm) margins. After adjusting for several clinicopathologic factors, there was a 69% relative reduction in risk associated with a > 10 mm negative margin width compared with positive margins.

Low-risk subsets of ductal carcinoma in situ: can radiation therapy be avoided?

In addition to evidence from MSK demonstrating a significant decline in LR over time in patients with DCIS treated with BCS [37], more recent prospective studies have similarly demonstrated a lower risk of LR in select modern cohorts of patients treated with BCS without RT compared with the initial randomized trials. These findings have garnered great interest in identifying a low-risk subset of patients in whom RT could be avoided following BCS.

A prospective study by Wong and colleagues [11], the ECOG-ACRIN E5194 study [10], and the Radiation Therapy Oncology Group (RTOG) 9804 study [9] all accrued patients with primarily small (≤2.5 cm), low–intermediate grade DCIS treated with BCS with a minimum of 3 mm margins. Notably, ECOG-ACRIN E5194 also enrolled patients with small-volume (≤1 cm), high-grade DCIS [10], and RTOG 9804 randomized patients to RT versus no RT [9]. Tamoxifen was prohibited in the Wong study, and used by 31% and 62% in the ECOG and RTOG studies, respectively. Overall, at a follow-up of 7 to 12 years, rates of LR among patients with low–intermediate grade DCIS treated with BCS alone ranged from 7% to 16% (Table 5),

Table 5
Outcomes of the modern prospective trials in patients with low-intermediate grade ductal carcinoma in situ treated with breast-conserving surgery alone

Study	Study dates	N	% Women using tamoxifen	Follow-up (y)	Local recurrence (No RT) (%)
Wong et al [11]	1995–2002	143	0	10	15.6
ECOG-ACRIN E5194 cohort 1 [10],[a]	1997–2002	561	31	12	14.4
RTOG 9804 (no-radiation group) [9],[b]	1998–2006	298	62	7	6.7

Abbreviations: BCS, breast-conserving surgery; DCIS, ductal carcinoma in situ; ECOG-ACRIN, Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group.

[a]Twelve-year local recurrence rate in the high-grade DCIS cohort was 24.6%.

[b]Seven-year local recurrence rate in the RT group was 0.6%.

Data from Early Breast Cancer Trialists' Collaborative G, Correa C, McGale P, et al. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010;2010(41):162–177.

much lower than the 28% 10-year rate of LR reported in the randomized trials for patients treated with BCS alone [16].

Although there is no debate that RT lowers LR risk in all patients with DCIS, the absolute risk of LR in select subsets of patients with non-high-grade DCIS may be sufficiently low that the benefit of RT is outweighed by the potential risks. Understanding LR risk for each individual patient is essential when making decisions regarding the need for adjuvant RT.

Predicting the risk of local recurrence: nomograms and genomic signatures

The prospective trials, along with large retrospective series, have shed light on the risk of LR following BCS for DCIS, which can vary significantly based on a variety of clinical and pathologic factors. Estimation of risk based on the original randomized trials of RT would likely result in overestimation of risk for many, and potential overtreatment. Individualizing risk allows clinicians to counsel patients about risks of recurrence after BCS alone and the additional benefit of adjuvant therapy to tailor therapy.

Rudloff and colleagues [41] developed a DCIS nomogram to better estimate risk of LR following BCS. The nomogram was developed from a cohort of 1681 patients with DCIS treated with BCS from 1991 to 2006, and uses 10 clinical, pathologic, and treatment variables to estimate the risk of LR and invasive recurrence at 5 and 10 years after BCS. Variables in the model include patient age, family history, year of surgery, clinical versus radiologic presentation, nuclear grade, necrosis, margins, and number of re-excisions (as a surrogate for tumor size). Once a patient's individual data are entered, the effect of adjuvant

therapy, including RT and endocrine therapy, can be added into the model to estimate benefit with each of these therapies. The model has been internally validated and demonstrates good discrimination (C-index 0.704; bootstrap corrected 0.688); external validation with independent populations has demonstrated similar results (C-index 0.63–0.92) [42–46].

Another method to estimate risk is with molecular profiling of the tumor. The Oncotype DX (Genomic Health, Redwood City, CA) DCIS score is a 12-gene assay that was developed to estimate LR risk in patients with DCIS treated with BCS. The DCIS score was validated using a subset of 327 patients from the ECOG-ACRIN E5194 study in whom tissue was available. In this cohort, the DCIS score was significantly associated with developing any LR (HR = 2.31, $P = .02$) as well as an invasive LR (HR = 3.68, $P = .01$) [47]. However, a "high" score was not associated with a higher LR risk than an intermediate score; in patients with low, intermediate, or high recurrence scores, the 10-year risk of LR was 10.6%, 26.7%, and 25.9%, respectively ($P \leq .0006$). Furthermore, the association with LR risk seemed to be predominantly limited to premenopausal women and those with DCIS size greater than 10 mm.

The Oncotype DCIS score was also assessed in 571 patients from Ontario with DCIS treated with BCS alone [48]. On multivariable analysis, a 50-point increase in the DCIS score was significantly associated with LR (HR = 1.68, $P = .02$). However, multifocality (HR = 1.97, $P = .003$), tumor size greater than 10 mm (HR = 2.07, $P = .01$), age less than 50 years (HR = 1.75, $P = .03$), and DCIS architecture (HR = 2.75, $P = .04$) each had a larger effect on LR risk than the DCIS score, suggesting that, in a heterogeneous DCIS population treated with BCS, clinicopathologic factors are needed to accurately estimate risk of LR.

PRESENT RELEVANCE

Concern for overtreatment

In 2015 Narod and colleagues [12] published a retrospective study using Surveillance, Epidemiology, and End Results data evaluating outcomes among 108,196 women treated for DCIS. The 20-year breast cancer mortality was 3.3%, irrespective of type of surgical treatment or the use of adjuvant therapy. Even though all women in this study received treatment of their DCIS that was appropriate for their clinical situation, many interpreted this study as evidence that DCIS is essentially a "non-lethal" disease that does not require treatment.

Natural progression

Although DCIS may be a nonobligate precursor to invasive carcinoma with a poorly understood natural history, clear evidence supports DCIS to be a precursor to invasive carcinoma versus a marker of increased risk. Studies of "benign" excisional biopsies that were re-reviewed decades later and found to contain DCIS demonstrated development of invasive carcinoma in the same breast as the initial DCIS lesion in 39% to 53% of patients [49–51]. In addition, evidence for progression to invasive carcinoma also comes from

prospective studies evaluating LR type after BCS for DCIS. In all of the randomized trials of RT [2–5,9,16], 50% of recurrences were invasive, suggesting that DCIS has the potential to invade. In addition, if DCIS were simply a high-risk lesion, the risk of LR would be unaffected by margin status following BCS, and the incidence of ipsilateral and contralateral cancers would be similar in patients with DCIS. Instead, the risk of LR is doubled in patients with positive versus negative margins [39,40], and ipsilateral invasive recurrences are four-fold higher than contralateral breast cancer incidence in patients with DCIS [16], confirming that DCIS is a true precursor lesion.

Studies of observation

Because of concerns regarding overdiagnosis and overtreatment of DCIS, coupled with the belief that some DCIS may not progress to invasive carcinoma in a woman's lifetime, there has been renewed interest in studying active surveillance in patients with low-risk DCIS as an alternative to surgery. Currently, there are 3 ongoing studies comparing surgery versus observation in women with low-risk DCIS: the surgery versus active monitoring for low-risk DCIS (LORIS) trial [14], the low-risk DCIS (LORD) trial [13], and the Comparison of Operative to Monitoring and Endocrine Therapy (COMET) trial (Table 6) [15].

A major concern regarding the trials of observation is whether these patients are in fact truly low risk for the development of invasive carcinoma. Pilewskie and colleagues [52] reviewed patients with DCIS diagnosed by core needle

Table 6
Eligibility criteria and primary endpoints for the LORIS, LORD, and COMET trials of surgery versus observation in low-risk ductal carcinoma in situ

	LORIS [14]	LORD [13]	COMET [15]
Age, y	≥46	≥45	≥40
Presentation	Screen-detected calcifications	Screen-detected calcifications	Screen-detected calcifications
DCIS grade	Non-high grade	Pure low grade	Non-high grade
Comedo necrosis	No	No	No
Hormone receptors	—	—	ER and/or PR ≥10%
Endocrine therapy	Allowed	Not allowed	Allowed
Primary endpoint	5-y ipsilateral invasive breast cancer-free survival	10-y ipsilateral invasive breast cancer-free survival	2-y ipsilateral invasive breast cancer-free survival

Abbreviations: COMET, Comparison of Operative to Monitoring and Endocrine Therapy; DCIS, ductal carcinoma in situ; ER, estrogen receptor; LORD, low-risk DCIS; LORIS, surgery versus active monitoring for low-risk DCIS; PR, progesterone receptor.

Data from Youngwirth LM, Boughey JC, Hwang ES. Surgery versus monitoring and endocrine therapy for low-risk DCIS: The COMET Trial. Bulletin of the American College of Surgeons 2017;102(1):62–63.

biopsy and subsequently treated at MSK between 2009 and 2012; they identified 296 patients who met LORIS criteria, which represented only 16% of the entire DCIS cohort. At surgical excision, 20% of the LORIS-eligible patients had invasive carcinoma that was not seen on core needle biopsy, suggesting that even low-risk patients with DCIS have a substantial upgrade rate to invasive carcinoma [52]. Furthermore, among women who remained LORIS eligible with pure DCIS even after excision, the 10-year rate of any LR after BCS alone was 12%, with a 6% risk of invasive recurrence [53]. Collectively, these findings reinforce that, outside of a clinical trial, surgical excision is warranted for all patients with biopsy-proven DCIS.

SUMMARY

The treatment of DCIS has evolved significantly over time, from mastectomy to BCS with RT, and now to consideration for BCS alone in select low-risk subsets of DCIS. Complete excision of disease is critical to minimize LR risk and, more importantly, invasive recurrence. With the understanding that LR risk after BCS is variable and influenced by several clinical and pathologic factors, treatment decisions are tailored to the individual patient based on risk estimation. RT reduces LR risk by half in all patients with DCIS following BCS, although the absolute benefit of this adjuvant therapy varies in each patient based on the individual risk. Because RT has no impact on breast cancer mortality, the risks and benefits of RT should be carefully weighed in each patient, particularly given its potentially serious associated side effects. Adjuvant endocrine therapy similarly reduces the risk of LR as well as the incidence of new contralateral cancers; however, the side-effect profile often limits compliance.

When counseling patients with DCIS, it is important to understand the wishes and priorities of the patient. A thorough discussion regarding the advantages and disadvantages of each treatment, as well as the impact of adjuvant therapies on recurrence risk, can help inform decision making so that patients can choose treatments that are best for them.

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