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ORIGINAL ARTICLE – BREAST ONCOLOGY

Outcomes for Women with Minimal-Volume Ductal Carcinoma In Situ Completely Excised at Core Biopsy

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ABSTRACT

Background. Overdiagnosis and overtreatment of ductal carcinoma in situ (DCIS) are concerns, especially for women with low-volume, screen-detected DCIS. This study aimed to evaluate the outcomes for such patients.

Methods. Women who had minimal-volume DCIS (mDCIS, defined as DCIS diagnosed by core biopsy but with no residual disease on the surgical excision) treated with breast-conserving surgery from 1990 to 2011 were identified. Ipsilateral and contralateral breast events (IBE and CBE) were compared by competing-risk (CR) analysis. Kaplan–Meier (KM) estimates and log-rank tests were used to evaluate covariates.

Results. The study identified 290 cases of mDCIS. The median age of the patients was 53 years. Radiation therapy (RT) was performed for 27.6% and endocrine therapy for 16.2% of the patients. The median follow-up period was 6.8 years. Overall, the IBE rates were 4.3% at 5 years and 12.3% at 10 years. Among the women not receiving RT, the 5- and 10-year IBE rates (5.4 and 14.5%) were higher than the CBE rates (1.8 and 2.7%). Among those receiving RT, the IBE rates (1.5 and 6.0%) were lower than the CBE rates (4.1 and 15.6%). The women receiving RT trended toward significantly lower IBE rates ($p = 0.07$). Age, grade, and endocrine therapy were not significantly associated with IBE risk.

Conclusions. Among the patients with mDCIS who did not receive RT, the IBE risk was substantially higher

than the CBE risk, demonstrating that even DCIS of very low volume is associated with clinically relevant disease. The finding that the IBE risk was greater than the CBE risk supports current strategies that treat DCIS as a precursor rather than a risk marker. Women with mDCIS are not at negligible risk for IBE in the absence of adjuvant therapy.

With the widespread adoption of screening mammography, ductal carcinoma in situ (DCIS) incidence has increased dramatically during the last 30 years, and currently accounts for 20% of all newly diagnosed breast cancers in the United States.[1] Due to advances in screening, DCIS is diagnosed not only more frequently, but also at smaller volumes.

For even very-low-volume DCIS, the standard treatment options are excision alone, excision with adjuvant radiation or endocrine therapy or both, and mastectomy. Although all the options result in excellent survival, the marked increase in diagnosis of DCIS of ever smaller volumes has raised concerns about both overdiagnosis and overtreatment. Thus, efforts have been made to identify subgroups of women with DCIS for whom excision alone is adequate.[2–4] Furthermore, clinical trials to evaluate DCIS outcomes managed with observation alone and no surgical excision are currently underway.[5–7]

Patients with minimal-volume DCIS (mDCIS), defined as disease completely excised by core biopsy, may represent a group at low risk for local recurrence after breast-conserving surgery (BCS), and their minimal-volume disease should possibly be considered a breast cancer risk factor rather than a true precursor lesion.

We hypothesized that patients with mDCIS who undergo BCS and no adjuvant therapy have a very low local recurrence risk, such that the risk of breast events in

the ipsilateral and contralateral breast is similar. We also evaluated the association of other clinical, pathologic, and treatment factors with ipsilateral events in these patients.

METHODS

After institutional review board approval, patients with mDCIS, defined as DCIS diagnosed by core biopsy with no residual disease at the time of surgical excision, who underwent BCS from 1990 to 2011 at Memorial Sloan Kettering Cancer Center were identified from a prospectively maintained database.

The variables examined were age, family history (≥ 1 first- or second-degree family member with breast cancer), nuclear grade (low vs intermediate/high), and use of adjuvant radiation therapy (RT) or endocrine therapy. Patients with markedly atypical ductal hyperplasia (ADH) bordering on or focally reaching DCIS (borderline lesions, $n = 58$) were included in the low-nuclear-grade category, as we could not definitively conclude that these lesions were not DCIS. Women were treated according to clinical judgment and patient preference; therefore it is likely that those judged to be at higher risk of recurrence more frequently received adjuvant therapies.

The patients were stratified by receipt of radiation. Correlations between receipt of RT and other patient characteristics were assessed using the chi-square test.

An event was defined as any subsequent ipsilateral local breast event (IBE) or contralateral breast event (CBE). A diagnosis of either DCIS or invasive cancer was considered an event. The time to the event was defined as the interval between the date of surgical excision and the first event.

Kaplan–Meier IBE estimates were calculated for the entire population of women with mDCIS by age, family history, nuclear grade, and adjuvant therapies. To avoid any potential bias related to inclusion of patients with borderline lesions, Kaplan–Meier IBE estimates were repeated, excluding the 58 borderline patients, and reported separately. Differences were assessed using the log-rank test.

Competing-risk analysis was used to evaluate the risk of IBE compared with CBE.[8] In this analysis, the endpoint was defined as the time interval from mDCIS BCS to the first event, either IBE or CBE. One patient had both an IBE and a CBE. The IBE occurred first and was therefore counted as an IBE for the competing-risk analysis.

The patients were censored at the date of mastectomy if it was performed after the initial BCS but before the development of any subsequent diagnosis of IBE or CBE.

All analyses were performed using SAS v9.4 and R v3.1.1. All p values lower than 0.05 were considered statistically significant.

RESULTS

From 1990 to 2011, among 3130 patients treated with BCS for DCIS, 290 cases of mDCIS were identified and constituted our study population. The median age of the patients was 53 years (range 26–86 years). Of the 290 patients, 80 (27.6%) received RT, and 47 (16.2%) received endocrine therapy. The characteristics of the entire population and the subsets that did and did not receive RT are summarized in Table 1. Those who received RT were more likely to have intermediate- or high-grade DCIS ($p < 0.0001$) and also more likely to receive adjuvant endocrine therapy ($p = 0.03$).

The median follow-up period was 6.8 years (range 0.02–23.8 years), with 65 patients followed for at least 10 years. An IBE occurred for 25 patients, of whom 8 had invasive cancer and 17 had DCIS. Seven of eight invasive IBEs were invasive ductal carcinoma. The diagnosis of the remaining IBE was unknown. The median time to invasive IBE was 78 months (range 13–138 months). Among the women receiving RT, three IBEs occurred, all of which were DCIS.

For the entire population of mDCIS patients, the Kaplan–Meier IBE rates were 4.3% at 5 years and 12.3% at 10 years (Fig. 1a). Age ($p = 0.44$) and nuclear grade ($p = 0.78$) were not significantly associated with IBE (Fig. 1b, c). Those who received RT trended toward a lower risk of IBE ($p = 0.07$), with a 10-year IBE rate of 6.5% compared with 14.7% for those not receiving RT (Fig. 1d). Only 47 women received endocrine therapy. The rate of IBE was not significantly lower in this small group (Fig. 1e). For the women who did not receive either adjuvant therapy ($n = 178$), the IBE rates were 5.7% at 5 years and 15% at 10 years. In contrast, none of the 19 women who received both RT and endocrine therapy experienced an IBE (Fig. 1f).

Excluding the 58 patients with borderline lesions, the IBE rate was 3.8% at 5 years and 12% at 10 years. Similar to the findings in the entire population, age ($p = 0.43$) and nuclear grade ($p = 1.0$) were not associated with IBE, whereas RT use trended toward a lower 10-year IBE rate (RT, 6.7% vs. no RT, 14.9%; $p = 0.08$). In the subset with borderline lesions excluded, the 10-year IBE rate was 7.4% with endocrine therapy and 13% without endocrine therapy ($p = 0.53$). Among those not receiving either adjuvant therapy ($n = 124$), the 10-year IBE rate was 14.7%. No woman with a borderline lesion received both RT and endocrine therapy.

Because women with intermediate or high-grade mDCIS more frequently received RT, we estimated IBE rates by nuclear grade after stratification by receipt of RT. Among those not receiving RT, 5- and 10-year rates of IBE were 4.3% and 13.9% for low grade (of whom over half were patients with borderline lesions), and 5.8% and 16.1% for intermediate/high-grade mDCIS ($p = 0.6$).

TABLE 1 Characteristics of the entire population of women with minimal-volume ductal carcinoma in situ (DCIS) stratified by receipt of radiation

Characteristic	Entire population (n = 290) n (%)	No radiation (n = 207)[a] n (%)	Radiation (n = 80)[a] n (%)	p Value[b]
Age (years)				0.8
≤49	108 (37)	77 (37)	31 (39)	
≥50	182 (63)	130 (63)	49 (61)	
Family history				0.1
No	171 (59)	128 (62)	42 (52)	
Yes	118 (40)	78 (37)	38 (48)	
Unknown	1 (1)	1 (1)	0 (0)	
Nuclear grade				<0.0001
Low[c]	122 (42)	107 (52)	14 (17)	
Intermediate/high	158 (55)	94 (45)	63 (79)	
Unknown	10 (3)	6 (3)	3 (4)	
Radiation therapy				–
No	207 (71)	207 (100)	–	
Yes	80 (28)	–	80 (100)	
Unknown	3 (1)	–	–	
Endocrine therapy				0.03
No	240 (83)	178 (86)	61 (76)	
Yes	47 (16)	27 (13)	19 (24)	
Unknown	3 (1)	2 (1)	0 (0)	

[a] Numbers do not sum up to 290 because for 3 women, receipt of radiation was unknown

[b] Chi-square test for correlation between receipt of radiation and other characteristics

[c] Low-nuclear grade includes markedly atypical ductal hyperplasia bordering on or focally reaching DCIS (n = 58)

A CBE occurred for 13 patients (10 invasive and 3 DCIS). Of 10 invasive CBEs, 9 were invasive ductal events, and 1 was an invasive lobular event. Among the 80 patients who received RT, 6 had invasive and 2 had DCIS CBE. Among the 207 patients not receiving RT, 4 had invasive and 1 had DCIS CBE. The median time to invasive CBE was 60 months (range 12–231 months). For the entire population, the Kaplan–Meier CBE rate was 2.5% at 5 years and 6.8% at 10 years.

Competing-risk analysis of IBE and CBE was performed. Among all the women with mDCIS, the cumulative incidence of IBE was higher than that of CBE (Fig. 2a). Among those not receiving RT, the risk for IBE was higher than the risk for CBE, whereas among those receiving RT, IBE was less frequent than CBE (Fig. 2b, c). Endocrine therapy reduced the incidence of both ipsilateral and contralateral breast events (Fig. 2d, e).
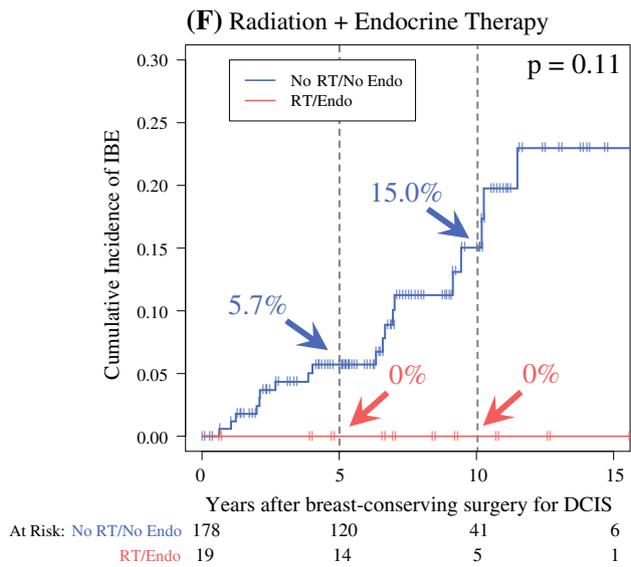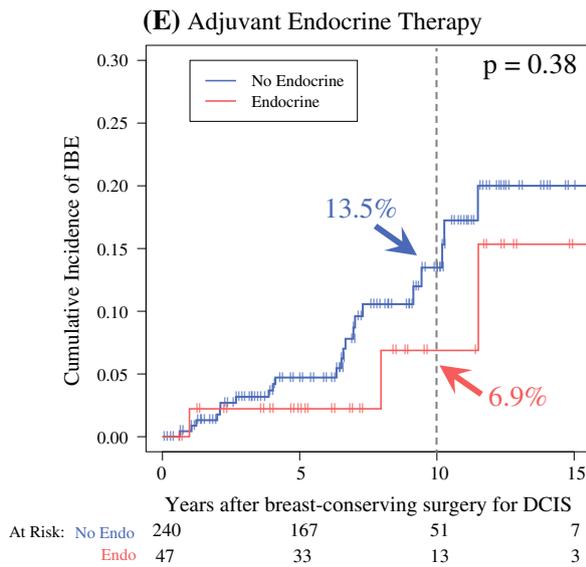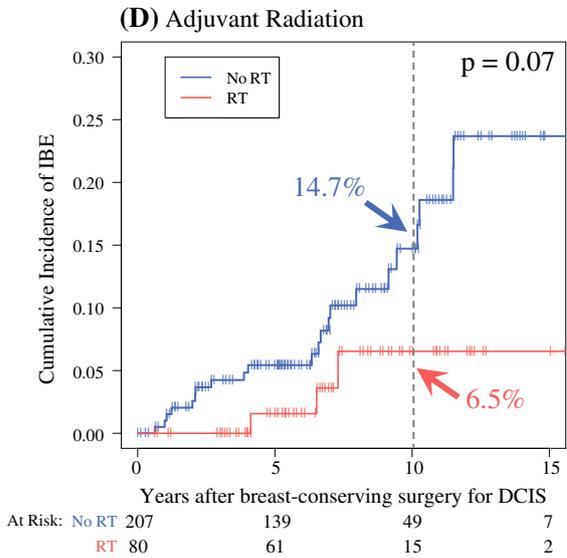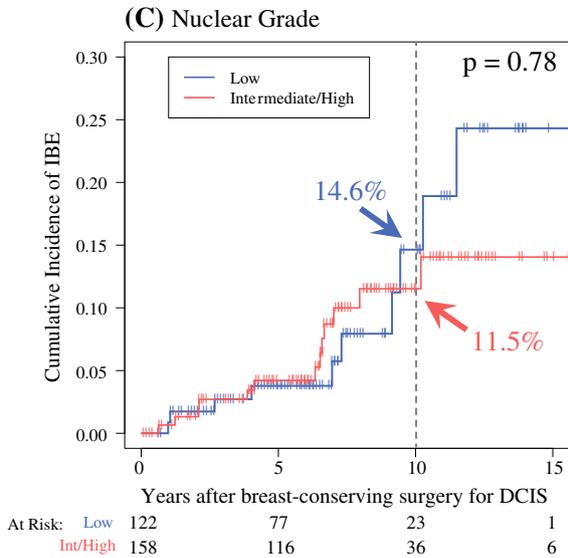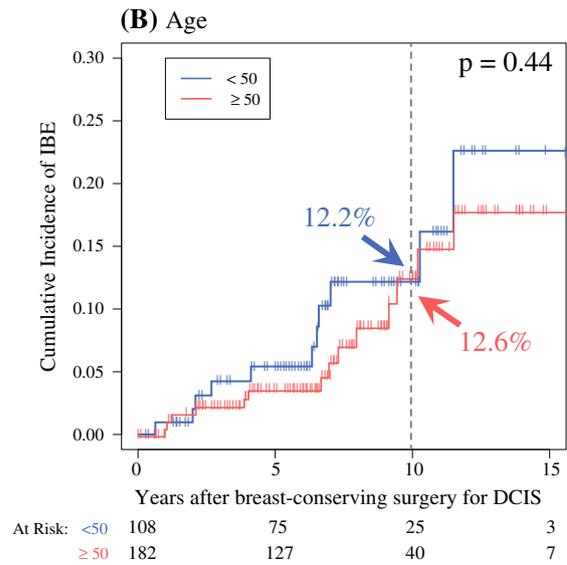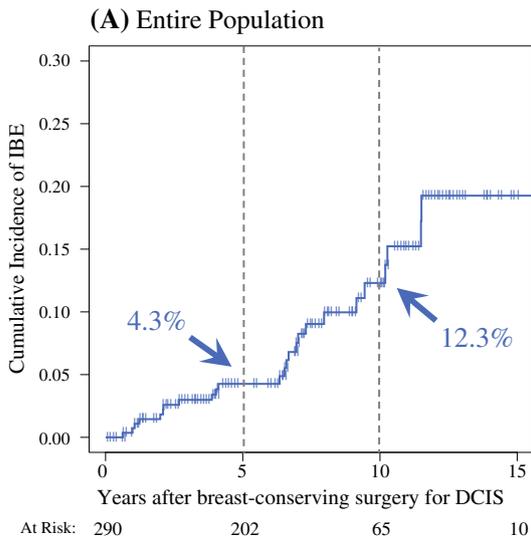
DISCUSSION

The optimal management of women with screen-detected DCIS remains controversial. Although randomized trials have shown that both adjuvant RT and endocrine therapy reduce local recurrence risk, neither has been shown to affect survival.[9–13] Additionally, each has potential morbidities. Whereas RT can increase cardiovascular morbidity and the risk of rare malignancies, endocrine therapy can cause vasomotor symptoms and an increased risk of thromboembolic events, endometrial cancer, arthralgias, or osteopenia, all of which raise concerns regarding overtreatment for DCIS.[14–20] Despite evidence from prospective studies that local recurrence rates after excision alone for select patients with DCIS are lower than in mature randomized trials,[2–4] identifying a subset of women with minimal risk of recurrence after surgical excision who do not benefit from adjuvant RT remains an unmet goal.

We hypothesized that patients with mDCIS (diagnosed at core biopsy with no residual disease at surgical excision) are at minimal risk of local recurrence after excision alone, and therefore garner minimal benefit from adjuvant therapy. Furthermore, we postulated that mDCIS may behave more like a risk factor for the development of breast cancer because the distinction between DCIS and ADH at small volumes (<2 mm) remains a diagnostic challenge.[21]

Results from 290 women with mDCIS did not support our hypothesis. Specifically, among the 178 who received

(A) Entire Population

Cumulative Incidence of IBE vs. Years after breast-conserving surgery for DCIS

4.3% at 5 years, 12.3% at 10 years

At Risk: 290 (0), 202 (5), 65 (10), 10 (15)

(B) Age

p = 0.44

< 50, ≥ 50

12.2% (<50), 12.6% (≥50)

At Risk: <50 108 75 25 3; ≥50 182 127 40 7

(C) Nuclear Grade

p = 0.78

Low, Intermediate/High

14.6% (Low), 11.5% (Int/High)

At Risk: Low 122 77 23 1; Int/High 158 116 36 6

(D) Adjuvant Radiation

p = 0.07

No RT, RT

14.7% (No RT), 6.5% (RT)

At Risk: No RT 207 139 49 7; RT 80 61 15 2

(E) Adjuvant Endocrine Therapy

p = 0.38

No Endocrine, Endocrine

13.5% (No Endocrine), 6.9% (Endocrine)

At Risk: No Endo 240 167 51 7; Endo 47 33 13 3

(F) Radiation + Endocrine Therapy

p = 0.11

No RT/No Endo, RT/Endo

5.7% and 15.0% (No RT/No Endo), 0% and 0% (RT/Endo)

At Risk: No RT/No Endo 178 120 41 6; RT/Endo 19 14 5 1

Ipsilateral breast events for women with minimal-volume DCIS. **a** The entire population, **b** by age, **c** by nuclear grade, **d** by receipt of radiation, **e** by receipt of endocrine therapy, and **f** by receipt of both radiation and endocrine therapy or neither

no adjuvant therapy, the 10-year Kaplan–Meier rate of IBE was 15%, similar to the 10-year local recurrence rate of 15.6% reported by Wong et al.[2] and the 12-year local recurrence rate of 14.4% reported by Solin et al.[3] in their modern prospective studies of excision alone for patients with low-risk, non–high-grade DCIS measuring 2.5 cm or smaller. This not-insignificant IBE rate observed in our patient population suggests the any volume of DCIS in the breast should be considered as clinically relevant disease.

Receipt of adjuvant therapy in this patient population was at the discretion of the treating physician and patient, and therefore reflects the perception of recurrence risk. For example, women with intermediate- or high-grade DCIS were much more likely to receive radiation (Table 1). Therefore, for this population, in which the use of radiation was not randomly assigned and the subset receiving RT had a higher risk of recurrence, the comparison of the RT and no-RT subsets underestimated the risk reduction due to radiation. The fact that the RT subset had a nearly significant lower rate of IBE although the patients were presumably at higher risk of recurrence demonstrates that even women with mDCIS experience a benefit from adjuvant RT. This is consistent with recent data from RTOG 9804 showing that for women with "good-risk" DCIS (defined as screen-detected, low- to intermediate-grade DCIS measuring <2.5 cm with ≥3-mm margins), randomization to adjuvant radiation resulted in a marked decrease in the 7-year local failure rate (6.7% without RT, 0.9% with RT; $p < 0.001$).[4] Our observation that RT was associated with a lower IBE risk is strengthened by our comparison of IBE and CBE, which used each patient as her own "control." Among the women not receiving RT, IBE was greater than CBE, but among the women receiving RT, IBE was less frequent than CBE, suggesting that RT effectively reduces excess ipsilateral risk associated with mDCIS.
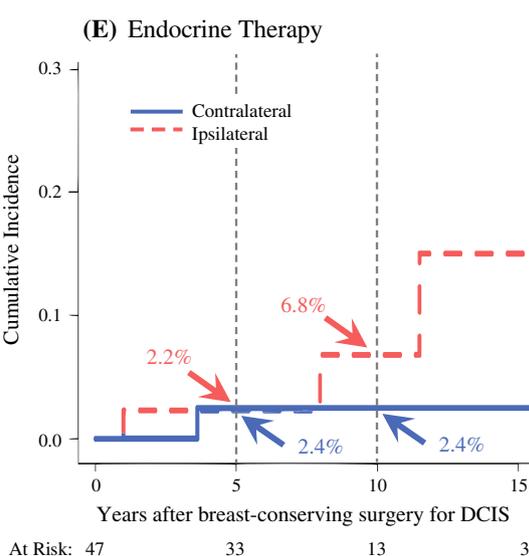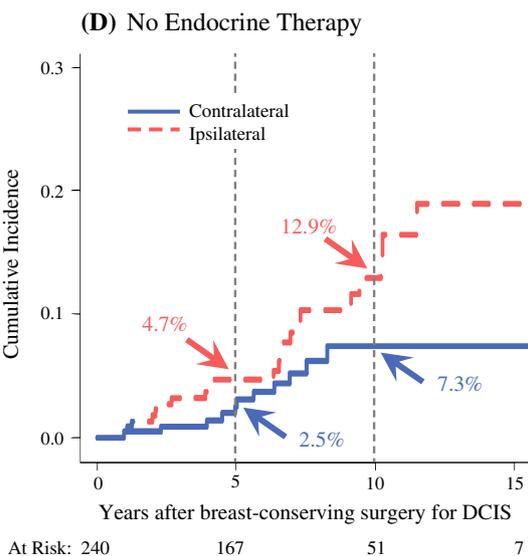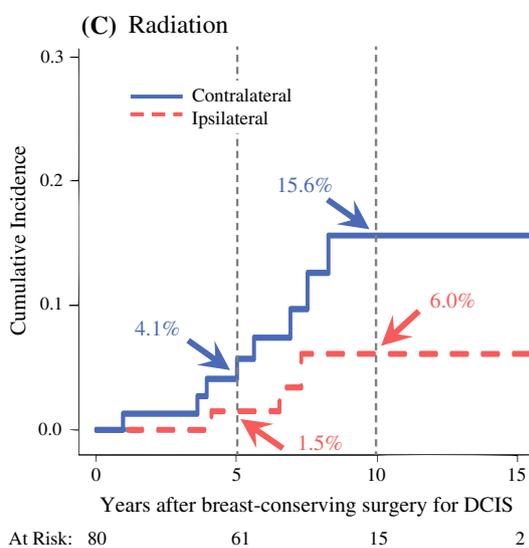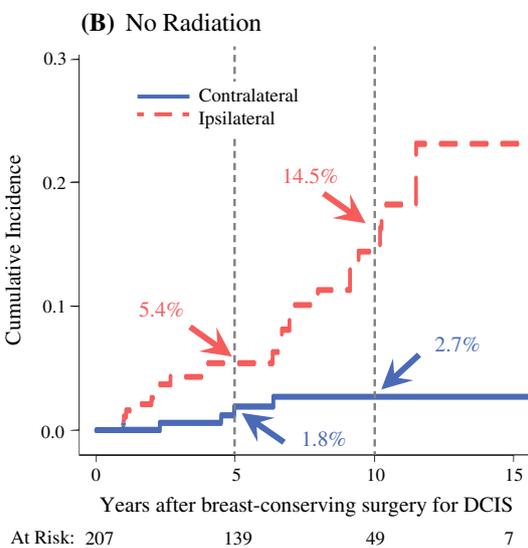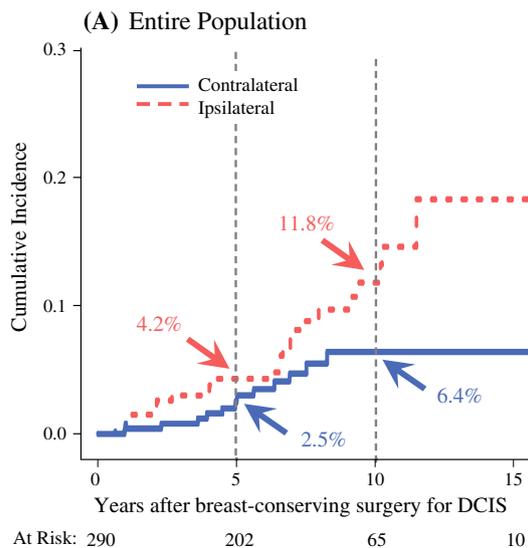
Not only have there been efforts to find DCIS subsets that do not benefit from adjuvant therapies, but there have also been recent arguments that select patients with non–high-grade DCIS should not be treated at all, as the possibility of progression to invasive carcinoma in these patients is uncertain. Currently, multiple randomized trials are evaluating active surveillance for women with low-risk DCIS.[5–7] The LORIS trial is studying the safety of observation alone for women with screen-detected non–high-grade DCIS diagnosed by core biopsy alone without subsequent excision. Its primary end point is the difference in

invasive breast cancer-free survival at 5 years between women treated with observation alone compared those who undergo standard surgical excision with and without adjuvant therapies.[6] The Low-Risk DCIS (LORD) trial is similar to LORIS but limited to women with low-grade lesions.[5] In the United States, the Comparison of Operative Versus Medical Endocrine Therapy for Low-Risk DCIS (COMET) trial compares standard operative treatment with nonsurgical management but encourages the use of endocrine therapy in the nonoperative arm of the study.[7] Such non-operative management should not be attempted outside of a clinical trial. Recent work by Pilewskie et al. showed that among women with DCIS who met LORIS eligibility requirements on core biopsy, 20% had invasive cancer found in the surgical excision specimen that was heterogeneous in grade, size, and receptor status.[22] Furthermore, among women with DCIS who continued to meet LORIS criteria even after examination of the complete surgical excision specimen, the 10-year IBE rate was a substantial 12.1%.[23]

Our current data show that the risk of IBE was clinically significant at 10 years in our entire population of women with very low-volume DCIS (IBE rate, 12.3%), in the subset of women 50 years of age or older (IBE rate, 12.6%), and in the subset of women with low-grade DCIS including cases borderline between ADH and DCIS (IBE rate, 14.6%). The 10-year IBE rate was 14.7% among our 207 mDCIS patients not receiving radiation, all of whom underwent surgical excision demonstrating complete DCIS removal by the core biopsy, and 13.9% in the subset with low-grade DCIS. All these findings suggest that identification of women with DCIS that can be observed without excision who will have minimal risk of subsequent IBE has not been achieved.

In our study population, we included 58 cases with a diagnosis of "markedly atypical ductal hyperplasia bordering on or focally reaching DCIS." These borderline lesions have been well studied and shown to defy clear categorization by expert breast pathologists even when they have been carefully instructed on diagnostic criteria and even in the modern era.[24–26] We recently examined the outcomes of all such borderline lesions treated at our institution from 1997 to 2010[27] and found that the 5-year rate of subsequent IBE for patients with borderline lesions was 7.7% versus 7.2% for those with clear DCIS ($p = 0.80$), and that the 5-year invasive IBE rate was 6.5% among those with borderline lesions and 2.8% for those with clear DCIS ($p = 0.25$), further suggesting that even these very-low-grade lesions have potential risk.

In the current analysis, all cases diagnosed as borderline between ADH and DCIS on core biopsy, but in which no residual lesion was found at excision, were included because at least some expert breast pathologists would

(A) Entire Population

(B) No Radiation

(C) Radiation

(D) No Endocrine Therapy

(E) Endocrine Therapy

◄**FIG. 2** Competing risk cumulative incidence of ipsilateral and contralateral breast events among women with minimal-volume ductal carcinoma in situ (DCIS) in **a** the entire population of women with minimal-volume DCIS, and women with minimal-volume DCIS receiving **b** no radiation, **c** radiation, **d** no endocrine therapy, or **e** endocrine therapy

classify them as DCIS, and we did not want to bias our population by excluding these cases presumably at low risk for subsequent IBE. To provide clarity, we repeated the IBE analysis in the subset created by excluding these borderline lesions and found no substantial change in our results.

We also compared IBE rates with CBE rates, reasoning that the contralateral breast should have the same risk as the ipsilateral breast if mDCIS has greater similarity to a breast cancer risk factor than to a precursor. However, we found that among those not receiving RT, the ipsilateral risk was much higher than the contralateral risk (14.5 vs 2.7% at 10 years), supporting the current strategy of treating even mDCIS as a precursor lesion rather than a risk factor.

Although relatively few invasive events occurred, some might argue that because the numbers of invasive IBEs and CBEs were similar, this provides evidence that DCIS is simply a bilateral risk marker. However, this argument is specious because we know that at least some DCIS lesions progress to invasive cancer, and in our population, the entire index mDCIS lesion was completely excised with widely clear margins. Furthermore, among those not receiving RT, the number of invasive IBEs was double that of invasive CBEs, whereas those receiving RT had no invasive IBE compared with six invasive CBEs. These data further support the conclusion that even mDCIS should be considered a precursor lesion.

Our analysis was retrospective, with all its associated limitations. The relatively small population with few events precluded multivariable analysis. However, to our knowledge, the current series is the only study reporting outcomes for mDCIS. Furthermore, the data were obtained from a robust, prospectively maintained database including detailed clinicopathologic data and ongoing follow-up information.

Finally, the observed risks of IBE in our population potentially provide conservative estimates for IBE after BCS for mDCIS due to inclusion of cases borderline between ADH and DCIS, which would be expected to bias our results toward a lower rate of IBE. This concern was addressed by repeating the IBE analysis with exclusion of all borderline lesions that demonstrated similar findings.

There has been great interest in exploring less-aggressive treatment for DCIS, both by omitting further adjuvant therapy after excision, whether radiation or endocrine therapy, and, most recently, by exploring elimination of surgery altogether for DCIS. However, our data further support the literature showing that no subsets of women with DCIS have been identified who have minimal risk of IBE or for whom adjuvant radiation does not lower IBE. Furthermore, our finding that IBE risk is greater than CBE risk supports the current standard strategy of treating DCIS as a precursor rather than a marker of risk.

The optimal approach for a woman with DCIS should include thorough discussion of the various treatment options, and the pros and cons of each option. A publicly available risk-estimation model (at www.nomograms.org) has been validated in at least five independent patient populations and provides an individualized risk estimate.[28–33] The risks and benefits of the various management options can then be weighed by the individual patient and her clinician, according to her values, with the goal of choosing the optimal treatment strategy.

CONCLUSIONS

Women with mDCIS completely removed at core biopsy and for whom surgical excision demonstrates no residual disease have a substantial risk of subsequent IBE that is higher than their risk in the contralateral breast, demonstrating that even very-low-volume DCIS is associated with clinically relevant disease. The finding that IBE risk is greater than CBE risk lends support to current strategies that treat DCIS as a precursor rather than a risk marker. In the current study, the women with mDCIS receiving RT experienced a lower risk of IBE than CBE, suggesting that RT effectively reduces the excess ipsilateral risk associated with mDCIS. These findings should be incorporated into the discussion weighing the pros and cons of the various management options for an individual woman with mDCIS.

DISCLOSURE There are no conflicts of interest.

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