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Outcomes of women with minimal volume ductal carcinoma in situ completely excised on core biopsy

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Abstract

Introduction—Overdiagnosis and overtreatment of ductal carcinoma in situ (DCIS) are concerns, especially in women with low-volume screen-detected DCIS. We sought to evaluate outcomes in such patients.

Methods—Women with minimal-volume DCIS (mDCIS, defined as diagnosed with DCIS by core biopsy but no residual disease on surgical excision) treated with breast-conserving surgery from 1990–2011 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—290 cases of mDCIS were identified; median age was 53yrs. 27.6% received radiation (RT); 16.2% received endocrine therapy. Median follow-up was 6.8 yrs. Overall, 5- and 10-yr IBE rates were 4.3% and 12.3%. Among women not receiving RT, 5- and 10-yr IBE rates (5.4% and 14.5%) were *higher* than CBE rates (1.8% and 2.7%); among those receiving RT, IBE rates (1.5% and 6.0%) were *lower* than CBE rates (4.1% and 15.6%). 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 patients with mDCIS not receiving RT, IBE risk was substantially higher than CBE risk, demonstrating that even DCIS of very low volume is associated with clinically relevant disease. The finding that IBE risk is greater than CBE risk supports current strategies that treat DCIS as a precursor rather than a risk marker. Women with mDCIS are not at negligible risk of IBE in the absence of adjuvant therapy.

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Keywords

minimal-volume ductal carcinoma in situ; low risk ductal carcinoma in situ; contralateral breast events; ipsilateral breast events; contralateral breast cancer; local recurrence; adjuvant radiation therapy; adjuvant endocrine therapy

INTRODUCTION

With the widespread adoption of screening mammography, ductal carcinoma in situ (DCIS) incidence has dramatically increased over the last 30 years, and now accounts for 20% of all newly diagnosed breast cancers in the U.S.¹ As advances have been made in screening, DCIS is diagnosed not only more frequently, but at smaller volumes. For even very low-volume DCIS, standard treatment options are excision alone, excision with adjuvant radiation or endocrine therapy or both, and mastectomy. Although all result in excellent survival, with the marked increase in diagnosis of DCIS of ever smaller volumes, concerns about both overdiagnosis and overtreatment exist. 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 without surgical excision are currently underway.^{5–7}

Patients with minimal volume DCIS (mDCIS), which we define as disease completely excised by core biopsy, may represent a group at low risk of local recurrence following breast-conserving surgery (BCS), and it is possible that their minimal-volume disease should be considered a breast cancer risk factor rather than a true precursor lesion. We hypothesized that patients with mDCIS treated with BCS and no adjuvant therapy would have a very low local recurrence risk, such that the risk of breast events in the ipsilateral and contralateral breast would be similar. We also evaluated the association of other clinical, pathological, and treatment factors with ipsilateral events in these patients.

METHODS

Following 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 1990–2011 at Memorial Sloan Kettering Cancer Center, were identified from a prospectively maintained database.

Variables examined included 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.

Patients were stratified by receipt of radiation. Correlations between receipt of RT and other patient characteristics were assessed using the χ 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. Time to event was defined as the interval between date of surgical excision and first event.

Kaplan-Meier IBE estimates were calculated for the entire population of women with mDCIS, and 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 these 58 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. Patients were censored at the date of mastectomy if performed after the initial BCS but before development of any subsequent diagnosis of IBE or CBE.

Analyses were conducted in SAS v9.4 and R v3.1.1. P-values <0.05 were considered statistically significant.

RESULTS

From 1990–2011, of 3130 patients treated with BCS for DCIS, 290 cases of mDCIS were identified and constitute our study population. Median age was 53 years (range 26–86). 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 were also more likely to receive adjuvant endocrine therapy ($p=0.03$).

Median follow-up was 6.8 years (range 0.02–23.8), with 65 patients having at least 10 years follow-up. An IBE occurred in 25 patients, of which 8 were invasive and 17 were DCIS. 7 of 8 invasive IBE were invasive ductal carcinoma; one was unknown. Median time to invasive IBE was 78 months (range 13–138). Among women receiving RT, there were 3 IBE, all of which were DCIS.

Five- and 10-year Kaplan-Meier IBE rates for the entire population of mDCIS were 4.3% and 12.3% (Fig. 1A). Age ($p=0.44$) and nuclear grade ($p=0.78$) were not significantly associated with IBE (Fig. 1B, 1C). Those who received RT trended toward a lower risk of IBE ($p=0.07$), with a 10-year IBE rate of 6.5% compared to 14.7% in 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). 5- and 10-year IBE rates for women who did not receive either adjuvant therapy ($n=178$) were 5.7% and 15.0%. In contrast, none of the 19 women who received both RT and endocrine therapy have experienced an IBE (Fig. 1F).

Excluding the 58 patients with borderline lesions, 5- and 10-year IBE rates were 3.8% and 12%. Similar to the findings in the entire population, age ($p=0.43$) and nuclear grade ($p=1.0$) were not associated with IBE, while RT use trended toward a lower 10-year IBE rate (6.7% [RT] vs 14.9% [no RT], $p=0.08$). In the subset with borderline lesions excluded, 10-year IBE rates were 7.4% with endocrine therapy, and 13.0% without ($p=0.53$); among those not receiving either adjuvant therapy ($n=124$), 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 ($p=0.6$).

A CBE occurred in 13 patients; 10 were invasive and 3 were DCIS. 9/10 invasive CBE were invasive ductal; one was invasive lobular. Among the 80 patients who received RT, there were 6 invasive and 2 DCIS CBE; in the 207 not receiving RT, there were 4 invasive and 1 DCIS CBE. The median time to invasive CBE was 60 months (range 12–231). Five- and 10-year Kaplan-Meier CBE rates for the entire population were 2.5% and 6.8%, respectively.

Competing risk analysis of IBE and CBE was performed. Among all women with mDCIS, cumulative incidence of IBE was higher than CBE (Fig. 2A). Among those not receiving RT, risk of IBE was higher than CBE, whereas in those receiving RT, IBE was less frequent than CBE (Fig. 2B, 2C). Endocrine therapy reduced the incidence of both ipsilateral and contralateral breast events (Fig. 2D, 2E).

DISCUSSION

The optimal management of women with screen-detected DCIS remains controversial. Although both adjuvant RT and endocrine therapy following BCS have been shown in randomized trials to reduce local recurrence risk, neither has been shown to affect survival.^{9–13} Additionally, each has potential morbidities. 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 following excision alone for select patients with DCIS are lower than in the mature randomized trials^{2–4}, identification of a subset of women with minimal risk of recurrence following surgical excision that does 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), would be at minimal risk of local recurrence following excision alone, and therefore would garner minimal benefit from adjuvant therapy. Further, we postulated that mDCIS may behave more like a risk factor for the development of breast cancer, since the distinction between DCIS and ADH at small volumes (<2mm) remains a diagnostic challenge.²¹

Results from 290 women with mDCIS did not support our hypothesis. Specifically, among the 178 who received no adjuvant therapy, the 10-year Kaplan-Meier rate of IBE was 15.0%, similar to the 15.6% 10-year local recurrence rate reported by Wong² and the 14.4% 12-year local recurrence rate reported by Solin³ in their modern prospective studies of excision alone in patients with low-risk, non-high-grade DCIS measuring ≤ 2.5 cm. This not-insignificant IBE rate observed in our patient population suggests any volume of DCIS in the breast should be considered 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, in this population in which the use of radiation was not randomly assigned and the subset that received RT had a higher risk of recurrence, the comparison of RT and no-RT subsets will underestimate the risk reduction due to radiation. The fact that the RT subset had a nearly significant lower rate of IBE despite the fact that those 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 that showed 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 7-year local failure rate (6.7% without RT, 0.9% with RT, $p<0.001$).⁴ Our observation that RT was associated with lower IBE risk is strengthened by our comparison of IBE to CBE, which used each patient as her own “control”. IBE was greater than CBE among women not receiving RT, but among 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. There are currently multiple randomized trials evaluating active surveillance in 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 with core biopsy alone without subsequent excision. Its primary endpoint is the difference in invasive breast-cancer-free survival at 5 years among women treated with observation alone compared with standard surgical excision with and without adjuvant therapies.⁶ The Low Risk DCIS (LORD) Trial is similar to LORIS, but is limited to women with low-grade lesions.⁵ In this country, the COMET trial compares standard operative treatment to non-surgical management, but encourages the use of endocrine therapy in the non-operative arm.⁷ Such non-operative management should not be attempted outside of a clinical trial, as recent work by Pilewskie 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 Further, 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 in our entire population of women with very low-volume DCIS, and in the subsets of those age ≥ 50 years and those with low-grade DCIS, risk of IBE was

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

In our study population, we included 58 cases diagnosed as “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 1997–2010²⁷ and found that the 5-year rate of subsequent IBE in patients with borderline lesions was 7.7%, versus 7.2% for those with clear DCIS ($p=0.80$), and with 5-year invasive IBE rates of 6.5% among those with borderline lesions and 2.8% for those with clear DCIS, respectively ($p=0.25$), 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 whom no residual lesion was found at excision, were included because at least some expert breast pathologists would classify them as DCIS, and we did not want to bias our population by excluding these cases that are 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 to CBE rates, reasoning that the contralateral breast should have the same risk as the ipsilateral breast if mDCIS is more similar to a breast cancer risk factor rather than a precursor. However, we found that among those not receiving RT, ipsilateral risk was much higher than contralateral—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 there were relatively few invasive events, some might argue that because the number of invasive IBE and CBE 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. Further, among those not receiving RT, the number of invasive IBE was double that of invasive CBE, while among those receiving RT, there were no invasive IBE compared with 6 invasive CBE. These data further support that even mDCIS should be considered a precursor lesion.

Our analysis was retrospective, with all associated limitations. The relatively small population with few events precluded multivariable analysis. However, the current series is the only report of outcomes for mDCIS we are aware of. Further, the data were obtained from a robust, prospectively maintained database including detailed clinicopathologic data and ongoing follow-up information. Lastly, 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 all borderline lesions excluded 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 there have been no identified subsets of women with DCIS that have minimal risk of IBE or for whom adjuvant radiation does not lower IBE. Further, 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 5 independent patient populations, and provides an individualized risk estimate.^{28–33} 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 on core biopsy and in 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. Women with mDCIS receiving RT experienced lower risk of IBE than CBE, suggesting that RT effectively reduces excess ipsilateral risk associated with mDCIS. These findings should be incorporated into the discussion of the pros and cons of the various management options for an individual woman with mDCIS.

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Synopsis

Among patients with minimal-volume DCIS, ipsilateral breast events in patients not receiving radiation therapy were substantially higher than contralateral breast events, demonstrating that even DCIS of very low-volume is associated with clinically relevant disease.

Fig 1.

Ipsilateral breast events for (A) the entire population of women with minimal-volume DCIS, and stratified by (B) age, (C) nuclear grade, (D) receipt of radiation, (E) receipt of endocrine therapy, and (F) receipt of both radiation and endocrine therapy or neither

Fig 2.

(A) Competing risk cumulative incidence of ipsilateral and contralateral breast events in women with minimal volume 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, and (E) endocrine therapy

TABLE 1
Characteristics of the entire population of women with minimal-volume DCIS, and stratified by receipt of radiation

Characteristic	Entire Population (N=290) N (%)	No Radiation (N=207) N (%)	Radiation (N=80) N (%)	p-value**
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 [§]	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%)	

* Numbers do not sum up to 290 because for 3 women receipt of radiation was unknown.

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

** χ^2 square test for correlation between receipt of radiation and other characteristics.