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Ductal Carcinoma In Situ and Margins <2 mm:

Contemporary Outcomes With Breast Conservation

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Abstract

Objective—To determine the relationship between negative margin width and locoregional recurrence (LRR) in a contemporary cohort of ductal carcinoma in situ (DCIS) patients.

Background—Recent national consensus guidelines recommend an optimal margin width of 2 mm or greater for the management of DCIS; however, controversy regarding re-excision remains when managing negative margins < 2 mm.

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Methods—One thousand four hundred ninety-one patients with DCIS who underwent breast-conserving surgery from 1996 to 2010 were identified from a prospectively managed cancer center database and analyzed using univariate and multivariate Cox proportional hazard models to determine the relationship between negative margin width and LRR with or without adjuvant radiation therapy (RT).

Results—A univariate analysis revealed that age <40 years ($n = 89$; $P = 0.02$), no RT ($n = 298$; $P = 0.01$), and negative margin width <2 mm ($n = 120$; $P = 0.005$) were associated with LRR. The association between margin width and LRR differed by adjuvant RT status (interaction $P = 0.02$). There was no statistical significant difference in LRR between patients with <2 mm and 2 mm negative margins who underwent RT (10-yr LRR rate, 4.8% vs 3.3%, respectively; hazard ratio, 0.8; 95% CI, 0.2–3.2; $P = 0.72$). For patients who did not undergo RT, those with margins <2 mm were significantly more likely to develop a LRR than were those with margins 2 mm (10-yr LRR rate, 30.9% vs 5.4%, respectively; hazard ratio, 5.5; 95% CI, 1.8–16.8, $P = 0.003$).

Conclusions—Routine additional surgery may not be justified for patients with negative margins <2 mm who undergo RT but should be performed in patients who forego RT.

Keywords

breast conservation; ductal carcinoma in situ; local regional recurrence; margins

Controversy regarding the optimal margin width for ductal carcinoma in situ (DCIS) has existed for several decades. The current consensus guidelines published by the Society of Surgical Oncology, American Society for Radiation Oncology, and American Society of Clinical Oncology recommend a margin threshold of 2 mm for DCIS. They also recommend the use of “clinical judgment” when determining whether patients with <2 mm margins should undergo re-excision, suggesting that patients who are at higher risk for recurrence should undergo re-excision.¹ The risk of local regional recurrence (LRR) in contemporary DCIS patients treated with breast conservation surgery (BCS) followed by radiation therapy (RT) ranges from 5% to 10% at 10 years.^{2–5} Half of the recurrences that do occur are invasive.^{6–10} There are many known risk factors for LRR, including age, family history, nuclear grade, comedonecrosis, RT, and margin status.^{5,10–12} Of these, only RT and margin status are modifiable.

Four randomized clinical trials in the 1980s and 1990s examined the role of RT as an adjunct to BCS.^{13–16} An overview of these early trials indicated that RT reduced the absolute 10-year risk of LRR by 15.2% (12.9% vs 28.1%, $P < 0.00001$).⁶ This benefit was seen regardless of age, tamoxifen use, tumor grade, comedonecrosis, tumor size, or margin status. While 3 of the 4 studies required negative margins for inclusion, the lack of standardized pathologic processing led to the inclusion of up to 18% of patients with positive or uncertain margins among the total population.¹⁷ In addition, varying thresholds and inconsistent pathologic processing were used to group margin status, making it difficult to draw conclusions about optimal margin width in patients undergoing RT.

Optimal margin width that can be regarded as negative without the need for re-excision is of great interest to surgeons as it is a modifiable risk factor for LRR. Two large meta-analyses

have demonstrated that positive margins definitively increase the risk of LRR in patients with DCIS who are treated with RT.^{18,19} Wang et al¹⁸ found that patients with negative margins had a significantly lower risk of LRR than did patients with positive margins [odds ratio (OR), 0.45; 95% confidence interval (CI), 0.36–0.57; $P < 0.001$]. Dunne et al¹⁹ found a similar reduction in risk among patients with negative margins (OR, 0.36; 95% CI, 0.27–0.47; $P < 0.0001$). On the basis of these data, it is widely accepted that positive margins increase the risk of LRR. However, the threshold for optimal margin width is still unclear because of a limited amount of data.

Current consensus guidelines²⁰ are based on grouped results from 4 studies that examined the outcomes of patients with margins of >0 or 1 versus ≤ 2 mm.^{21–24} Three of the 4 studies included historical cohorts dating back to the 1970s and were associated with significantly higher LRR rates than those currently seen in the modern era, with advances in breast imaging, standardized tissue processing, and utilization of RT. While the guidelines recommend the use of “clinical judgment,” emphasizing patient-centered evaluations for patients with margins < 2 mm, many multidisciplinary breast practitioners use this guideline as an absolute indication for re-excision. Therefore, in this study, we examined a contemporary cohort of DCIS patients who underwent standardized imaging, pathologic, and RT techniques to determine the risk of LRR among patients with close negative (< 2 mm) versus free margins (≥ 2 mm) who did or did not undergo RT.

METHODS

After receiving IRB approval, we identified 1503 patients who had been diagnosed with pure DCIS from January 1, 1996 to December 31, 2010 at The University of Texas MD Anderson Cancer Center (Houston, TX) and who had been identified via the prospectively managed MD Anderson Breast Cancer Management System Database. Only patients who had undergone BCS were included in the study. Patients who had undergone mastectomy and those whose surgical pathologic results were not reviewed at MD Anderson were excluded (Fig. 1). Demographic, clinical, pathologic, treatment, and follow-up variables were analyzed with respect to margin status at the time of definitive surgery for treatment of the initial diagnosis of DCIS. Patients with close margins (< 2 mm) and free margins (≥ 2 mm) were included. Patients with positive margins ($n = 12$) were excluded. Patients with close margins (< 2 mm) were divided into 2 groups, 0.01 to 1.00 mm and 1.01 to 1.99 mm for subgroup analysis.

Institutional standards for pathologic specimen processing were similar throughout the study period. Lumpectomy specimens had been inked with 6 different colors to separately identify each face of the specimen. The specimens had then been sectioned into 3 to 5-mm slices. The pathologist grossly examined each slice to determine the proximity of the lesion of concern to the margins. The slices had then been laid out sequentially in a standardized fashion and radiographed. A formal radiograph review was performed by the radiologist to determine the extent of radiographic abnormalities and their proximity to the margins. If concerning, a frozen section analysis had been performed, and if indicated, additional tissue margin had been excised. The final margin width had been based on an examination of formalin fixed, routinely processed, and paraffin-embedded tissue sections. The number of

sections evaluated had been determined by the extent of gross and radiologic tissue abnormalities. The final margin width was reported in millimeters. In 2003, estrogen receptor status evaluated by immunohistochemistry became routinely incorporated into pathologic evaluation of DCIS cases; these data were also included and analyzed in our study.

Most patients [1193 (80%)] underwent RT following surgery. Of these, 38 patients in clinical trials underwent brachytherapy. The remainder underwent standard external beam RT. During the study period, RT following BCS at our institution consisted of 50 Gy in 25 fractions to the whole breast, followed by a tailored 10 to 14 Gy boost to the tumor bed (14 Gy in 7 fractions for patients with close margins <2 mm and 10 Gy in 5 fractions for patients with more widely negative margins).

Statistical Analyses

Chi-square test or Fisher exact test was used to test the differences among categorical variables. Wilcoxon rank-sum test and Kruskal–Wallis test were used to detect differences among continuous variables. The distribution of time to LRR was estimated using the Kaplan–Meier method. Log-rank tests were performed to test the differences in survival between groups. Cox regression models were used to investigate the association between margin width and LRR while adjusting for other baseline variates. Patients who did not experience a LRR were censored at the time of last contact or death. A multivariate Cox proportional hazards model was developed by first including adjuvant RT and margin width in the univariate analysis, regardless of their *P* values, along with a set of candidate predictor variables with *P* values <0.10. A backward elimination was then performed, using 0.05 for the significance level of the Wald chi-square, to determine which effects remained in the final model. We further assessed the interaction effect of adjuvant RT and margin width on LRR. The purpose of this analysis was to determine whether the magnitude or direction of the association between margin width and LRR differed with the use of adjuvant RT. Martingale residuals were used to check the Cox proportional hazards model assumption for the continuous variables, including age at diagnosis and pathologic tumor size.^{25–28} All statistical computations were performed using SAS software version 9.4 and S-Plus version 8.2.

RESULTS

Baseline patient, tumor, and treatment characteristics were examined (Table 1). The median follow-up time was 8.7 years. Overall, the median age was 56 years (range, 18–89 yrs). Most patients [1193 (80%)] underwent adjuvant RT, and (44.9%) received adjuvant hormonal therapy. Most patients (1371, 92.0%) had free margins (≥ 2 mm) on final pathologic analysis, and 120 had close negative margins (<2 mm). Of the patients with close margins, 99 had margins of 1 mm and 21 had margins of 1 to 2 mm. Of the patients with close negative margins of < 2 mm, 89 patients had only 1 close negative margin, 22 patients had 2 close negative margins, and 9 patients had ≥ 3 close negative margins. Overall, 3.4% of patients (51 of 1491) had an LRR.

In comparison to patients who did not undergo RT, patients who underwent RT were more likely to have tumors >1 cm, high nuclear grade (III), comedonecrosis, and have undergone adjuvant hormonal therapy. The median age of patients undergoing RT was 55 years versus 58 years for patients not undergoing RT ($P = 0.004$). The median pathologic tumor size in patients undergoing RT was 1.0 cm versus 0.6 cm in patients not undergoing RT ($P = 0.001$). Patients who underwent adjuvant hormonal therapy were more likely to have also undergone adjuvant RT. Patients undergoing adjuvant hormonal therapy were more likely to have hormone receptor-positive disease and a low nuclear grade (I or II).

Age <40 years and adjuvant RT were associated with increased LRR on the basis of the univariate Cox proportional hazards model (Table 2). Interaction effects between margin width and adjuvant RT, or adjuvant hormone therapy were investigated in the multivariable Cox model adjusting for age. There was a statistically significant interaction effect for margin width and adjuvant RT ($P = 0.02$). The final multivariate Cox proportional hazards model included age, margin width, adjuvant RT, and the interaction between margin width and RT. Among patients who underwent adjuvant RT, patients with a negative margin width of <2 mm had no significantly higher risk of LRR than did those with ≥ 2 mm [hazard ratio (HR), 0.77; 95% CI, 0.19–3.23, $P = 0.72$] (Table 3). However, patients who did not undergo adjuvant RT had a significantly higher risk of LRR (HR, 5.49; 95% CI, 1.79–16.88, $P = 0.003$) (Table 3). Furthermore, patients with close negative margins ($n = 99$) of 0.01 to 1.00 mm had a further increased risk compared with those with ≥ 2 mm for LRR among patients who did not undergo adjuvant RT (HR, 7.18; 95% CI, 2.34–21.98, $P = 0.0006$). This risk was not seen in patients with margins of 0.01 to 1.0 mm who underwent RT (HR, 1.15; 95% CI, 0.31–4.28, $P = 0.84$).

Figure 2 shows Kaplan–Meier plots for LRR among patients with close negative versus free margins among all patients, patients who underwent RT, and patients who did not undergo RT. While there was no difference in the incidence of LRR among patients with close negative versus free margins in the overall cohort, there was a significant difference when the cohort was separated into patients who did and did not undergo RT. This difference was not seen among patients who underwent RT (Table 4).

We calculated 10-year LRR rates for patients who had and had not undergone adjuvant RT. Among patients who had undergone RT, there was no significant difference in the 10-year LRR among patients with close margins and patients with free margins (4.8% vs 3.3%). However, among patients who did not undergo RT, there was a significant difference in 10-year LRR (30.9% vs 5.4%). Patients ≤ 40 years who had undergone RT had a 10% risk of LRR at 10 years compared with 3% in patients aged >40 years ($P = 0.03$). This difference in 10-year LRR remained for patients aged ≤ 40 years versus >40 years who did not undergo RT (15.6% vs 6.2%) but was not statistically significant.

DISCUSSION

On the basis of the results of this large single-center, contemporary study of patients with DCIS who underwent BCS with standardized imaging, pathologic processing, surgical, and RT techniques, we conclude that patients aged <40 years and patients who do not undergo

RT with margins < 2 mm are at the highest risk of LRR. To our knowledge, this is the largest contemporary study to specifically examine the difference in LRR among patients with pure DCIS who underwent BCS with close negative versus free margins. Like many previous studies, we found that age, RT, and margin width had a significant effect on LRR. Furthermore, we found no difference in LRR among patients undergoing RT with close versus free margins. However, there was a significant increase in the 10-year LRR rate among patients who did not undergo adjuvant RT. To further investigate this increased risk, we subdivided the close margin group and examined risk by margins of 0 to 1 mm. The increased risk of LRR was even higher among these patients who did not undergo RT, and was not seen in patients who had undergone RT. In multivariate analyses, age < 40 years was an independent risk factor for LRR among patients who underwent RT compared with age > 40 years; these findings indicate that additional multidisciplinary considerations for re-excision are warranted for margins < 2 mm in these patients.

A recent study-level meta-analysis by Marinovic et al²⁰ examined the association between surgical margins and LRR in women with DCIS who had been treated with BCS. Twenty retrospective studies performed over a 50-year period (1968–2010) met the inclusion criteria, and 7883 patients were included. The median mid-point year for studies included in the meta-analysis was 1991. The prevalence of LRR was 8.3%, with a median follow-up of 6.5 years. Overall, 71% of patients underwent whole-breast RT, and 20.8% of patients underwent endocrine therapy. Using random effects logistic metaregression modeling, the OR for the LRR rate between the negative versus positive or close margin groups was 0.53 (95% CI, 0.45–0.62; $P < 0.001$). The definition of a positive margin was highly variable among studies, and there was no standardized pathologic processing method among the different studies. A positive margin was defined as 0 mm in 9 studies, < 1 mm in 7 studies, < 2 mm in 3 studies, and < 3 mm in 1 study.

Because of the discrepancy in definition of positive margins, a Bayesian network meta-analysis was used to allow single and multiple cut-points per study. Four studies were identified to compare LRR rates among patients with margins of > 0 or 1 mm compared with 2 mm.^{20–24} ORs with 95% credible intervals were calculated for patients with negative margins relative to those with positive margins. For patients with negative margins of > 0 or 1 mm, the OR was 0.45 (95% CrI, 0.32–0.61) compared with that for patients with positive margins. For patients with negative margins of < 2 mm, the OR was 0.32 (95% CrI, 0.21–0.48). These findings did not differ when patients who did not undergo RT were excluded. The difference in ORs between these 2 groups was quite small, and the authors acknowledged that the model may have exaggerated the differences among smaller threshold categories, such as > 0 or 1 and 2 mm in this example.

Of the 4 studies, 3 included patients dating back to the 1970s. Using a multivariable Cox regression analysis to study the association between margin width and recurrence, investigators at Memorial Sloan-Kettering Cancer Center found a significantly higher risk of LRR (HR, 1.47) among patients who underwent surgery between 1978 and 2000 than among patients who underwent surgery between 2001 and 2010 ($P = 0.002$).²¹ When stratifying patients by time period, the risk of LRR was increased among the older cohort of patients who underwent surgery but not RT between the years 1978 to 2000 compared with

patients treated between 2001 and 2010 (HR, 1.60; $P=0.003$). Similar to our study, Van Zee et al found that there was no significant difference in the LRR rate between patients who underwent RT with close margins (≤ 2 mm) and those with wide margins ($>2-10$ mm) (HR, 0.95 vs 1.00; $P=0.95$). In contrast, patients who did not undergo adjuvant RT had a slightly higher risk of LRR with close margins than with larger margins (HR, 0.75 vs 0.58; $P<0.0001$).

In our previous smaller study reported in 2012 on patients with DCIS who underwent BCS from 1996 to 2009, age <40 years, pathologic tumor size ≤ 1.5 cm, and no RT were associated with a significantly higher LRR rate on univariate analysis.²⁹ On multivariate analysis, these 3 variables were associated with an increased HR for LRR, which remained statistically significant. In that study, margins were grouped into negative versus close or positive, and there was no statistically significant difference in the LRR rate between the 2 groups. This is likely because only 4 patients had positive margins, and most patients (80.3%) underwent RT. The study reported in 2012 was not included in the recent meta-analysis. In the current study, the number of patients included was larger and the median length of follow-up time was longer. Patients with positive margins were excluded, and patients with close negative stratified by degree of margin width versus free margins were compared. Given the interaction effect between RT and margins, LRR rates were dramatically higher in younger patients with close margins than in those with free margins who did not undergo RT. However, this difference was not seen among patients who underwent RT. Taking the results of the present study together with the Early Breast Cancer Trialists' Collaborative Group overview of trials in radiotherapy for DCIS (which did not specifically address width of negative margins), there appears to be no independently associated risk of local recurrence by younger age among patients not receiving radiotherapy but a significant reduction in local recurrence risk for older compared with younger women who receive radiotherapy for DCIS.⁶

Recent consensus guidelines from the Society of Surgical Oncology, American Society for Radiation Oncology, and American Society of Clinical Oncology recommend the standard use of a 2-mm margin in DCIS patients undergoing BCS and whole-breast RT.¹ They recommend using clinical judgment when determining the need for surgery in patients with margins between 0 and 2 mm. The decision to use the 2 mm threshold rather than >0 mm was based on the results of the meta-analysis discussed above, with weak evidence of a reduction in LRR among patients with margins >2 mm found in the Bayesian model (ROR, 0.72; 95% CrI, 0.47–1.08), which did not reach statistical significance.

One important caveat and potential limitation of our study is that our findings may not be broadly applicable to patients who are treated at other centers or who undergo components of their diagnosis and therapy at multiple different centers that do not use similar multidisciplinary practice guidelines. Although the number of patients in the less than 2 mm group is modest, this number of patients is not small and the comparison group with margins 2 mm and greater is large. Therefore it is hard to argue that a larger sample size will demonstrate a significant difference between two different margin groups among RT patients. A cautionary note on this observation is the modest number of patients in the cohort with less than 2 mm margins together with an overall low rate of LRR, so that it can be

underpowered to detect a small difference in LRR between free and close margin groups. Our findings suggest that patients with close margins (<2 mm) who forego RT should undergo re-excision to achieve margins of 2 mm. In patients undergoing RT, re-excision offers no benefit in the 10-year LRR rate in patients with close negative margins compared with that in patients with free margins. Together with the present findings, the new consensus guidelines provide surgeons and multidisciplinary teams with a potential framework for individualizing therapy, weighing the potential risks versus benefits of additional surgery against the absolute risk of LRR, which are likely to be higher in patients <40 years, those with multiple close margins, and those foregoing RT. Finally, in the case of close but negative margins, postsurgical mammography is indicated to ensure the complete excision of malignant-appearing calcifications. Further contemporary multicenter, prospective studies with additional follow-up are needed to ensure that the findings of this study are applicable to a large, more heterogeneous population.

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FIGURE 1.

Inclusion criteria flowchart. All patients with pure DCIS diagnosed during the study period were identified. Patients without review of final pathology, undergoing mastectomy, final positive margins, or final margins unable to be assessed were excluded. BCS indicates breast conserving surgery.

FIGURE 2.

Local regional recurrence among patients with DCIS treated with breast conserving surgery with and without radiation therapy. A, All patients. B, Patients with RT. C, Patients without RT. Green line represents patients with margins < 2 mm. Blue line represents patients with margins ≥ 2 mm.

TABLE 1

Demographic, Tumor, and Treatment Characteristics of Patients Who Underwent Breast-conserving Surgery

Characteristic	Entire Study Cohort, n (%) * (n = 1491)	Radiation Therapy, n (%) * (n = 1193)	No Radiation Therapy, n (%) * (n = 298)
All patients	1491	1193	298
Median age, yr (range)	56 (18–89)	55 (23–86)	58 (18–89)
40	89 (6.0)	72 (6.0)	17 (5.7)
>40	1402 (94.0)	1121 (94.0)	281 (94.3)
Menopausal status			
Pre	354 (23.7)	291 (24.4)	63 (21.1)
Post	1126 (75.5)	892 (74.8)	234 (78.5)
Peri	5 (0.3)	4 (0.3)	1 (0.3)
Unknown	6 (0.4)	6 (0.5)	0 (0.0)
Family history			
No	810 (54.3)	663 (55.6)	147 (49.3)
Yes	681 (45.7)	530 (44.4)	151 (50.7)
First degree			
No	1209 (81.1)	979 (82.1)	230 (77.2)
Yes	281 (18.9)	213 (17.9)	68 (22.8)
Nuclear grade			
Low/intermediate	809 (54.3)	592 (49.6)	217 (72.8)
High	647 (43.4)	579 (48.5)	68 (22.8)
Unknown	35 (2.3)	22 (1.8)	13 (4.4)
Median tumor size, cm (range)	1.0 (0.01–12.5)	1.0 (0.01–12.5)	0.6 (0.05–6.6)
1 cm	670 (44.9)	506 (42.4)	164 (55.0)
>1 cm	502 (33.7)	451 (37.8)	51 (17.1)
Unknown	319 (21.4)	236 (19.8)	83 (27.9)
Comedo			
Absent	1023 (68.6)	789 (66.1)	234 (78.5)
Present	393 (26.4)	342 (28.7)	51 (17.1)
Unknown	75 (5.0)	62 (5.2)	13 (4.4)
Necrosis			
Absent	948 (63.6)	735 (61.6)	213 (71.5)
Present	520 (34.9)	443 (37.1)	77 (25.8)
Unknown	23 (1.5)	15 (1.3)	8 (2.7)
RT			
No	298 (20.0)	—	—
Yes	1193 (80.0)	—	—
Hormone therapy			
No	822 (55.1)	600 (50.3)	222 (74.5)
Yes	669 (44.9)	593 (49.7)	76 (25.50)
Estrogen receptor status			

Characteristic	Entire Study Cohort, n (%) [*] (n = 1491)	Radiation Therapy, n (%) [*] (n = 1193)	No Radiation Therapy, n (%) [*] (n = 298)
Positive	849 (56.9)	704 (59.0)	145 (48.7)
Negative	157 (10.5)	138 (11.6)	19 (6.4)
Unknown	485 (32.5)	351 (29.4)	134 (45.0)
Margin width			
Close (<2 mm)	120 (8.1)	100 (8.4)	20 (6.7)
Free (≥ 2 mm)	1371 (91.9)	1093 (91.6)	278 (93.3)

^{*} Except where indicated.

TABLE 2

Univariate Analysis of the Association Between Clinical and Pathologic Factors and Local Regional Recurrence

Variable	Hazard Ratio	95% Confidence Interval	P Value
Age, yrs			
40	1.00 (reference)	—	—
>40	0.4	0.18–0.88	0.02
Family history			
No	1.00 (reference)	—	—
Yes	1.19	0.69–2.07	0.53
First degree			
No	1.00 (reference)	—	—
Yes	0.82	0.39–1.75	0.61
Nuclear grade			
Low or intermediate	1.00 (reference)	—	—
High	1.03	0.59–1.79	0.93
Tumor size			
1 cm	1.00 (reference)	—	—
>1 cm	1.52	0.80–2.90	0.2
Comedo			
Absent	1.00 (reference)	—	—
Present	0.77	0.40–1.51	0.45
Necrosis			
Absent	1.00 (reference)	—	—
Present	0.67	0.36–1.26	0.22
Radiation therapy			
Yes	1.00 (reference)	—	—
No	2.28	1.28–4.05	0.01
Hormone therapy			
No	1.00 (reference)	—	—
Yes	0.63	0.35–1.13	0.12
Hormone receptor status			
Positive	1.00 (reference)	—	—
Negative	0.75	0.22–2.50	0.64
Margin width			
Free (≥ 2 mm)	1.00 (reference)	—	—
Close (<2 mm)	1.7	0.73–4.00	0.22
Margin width			
Free (≥ 2 mm)	1.00 (reference)	—	—
Close (1.1–1.9 mm)	0.81	0.05–13.7	0.88
Closest (≤ 1 mm)	2.21	0.96–5.09	0.17

TABLE 3

Multivariate Cox Proportional Hazard Models of Local Regional Recurrence Among Patients Who Did and Did Not Undergo Radiation Therapy *

Variable	Hazard Ratio	95% Confidence Interval	P Value
Radiation therapy			
Age, yrs			
>40	1.00 (reference)		
40	2.72	1.05–7.06	0.04
Margin width			
Free (≥ 2 mm)	1.00 (reference)		
Close (<2 mm)	0.77	0.19–3.23	0.72
No radiation therapy			
Age, yrs			
>40	1.00 (reference)		
40	2.08	0.48–9.08	0.33
Margin width			
Free (≥ 2 mm)	1.00 (reference)		
Close (<2 mm)	5.49	1.79–16.88	0.003

* Variables in the model included: age, radiation therapy, margin width.

TABLE 4

Predictors of 10-yr Local Regional Recurrence Rates in Patients With Ductal Carcinoma In Situ Treated With Lumpectomy, With and Without Radiation Therapy

Predictor	Adjuvant Radiation Therapy			No Adjuvant Radiation Therapy		
	Events/Total	10-Yr Local Regional Recurrence Rate	P Value	Events/Total	10-Yr Local Regional Recurrence Rate	P Value
All patients	33/1193	3.5% (2.4%, 5.1%)		28/298	6.7% (4.2%, 10.7%)	
Age, yrs						
40	5/72	10.0% (4.1%, 23.5%)	0.03	2/17	15.6% (4%, 50.7%)	0.26
>40	28/1121	3.0% (2%, 4.6%)		16/281	6.2% (3.8%, 10.2%)	—
Family history						
No	15/662	2.4% (1.3%, 4.2%)	0.19	11/147	7.7% (4.2%, 13.9%)	0.35
Yes	18/530	4.9% (3%, 8.1%)		7/151	5.8% (2.8%, 12%)	—
First degree relative with breast cancer						
No	28/979	3.4% (2.2%, 5.1%)	0.74	15/230	6.9% (4.1%, 11.5%)	0.54
Yes	5/213	3.9% (1.6%, 9.4%)		3/68	6.0% (1.9%, 18%)	—
Nuclear grade						
Low or intermediate	17/592	3.8% (2.2%, 6.4%)	0.98	11/217	5.5% (3%, 10%)	0.19
High	16/579	3.2% (1.8%, 5.5%)		6/68	10.9% (4.9%, 23.4%)	—
Tumor size						
1 cm	8/506	1.5% (0.7%, 3.2%)	0.055	10/164	6.5% (3.4%, 12.2%)	0.42
>1 cm	15/451	4.1% (2.3%, 7.3%)		4/51	10.6% (4.1%, 26.3%)	—
Comedo						
Absent	26/789	2.6% (1.2%, 5.7%)	0.39	14/232	6.8% (4%, 11.5%)	0.62
Present	7/342	4.0% (2.6%, 6.3%)		4/51	8.3% (3.2%, 20.6%)	—
Necrosis						
Absent	22/735	4.0% (2.6%, 6.3%)	0.8	16/213	8.0% (4.9%, 13%)	0.16
Present	11/443	2.4% (1.2%, 4.6%)		2/77	3.4% (0.8%, 13.4%)	—
Hormone therapy						
No	20/600	4.3% (2.7%, 6.8%)	0.34	14/222	7.6% (4.5%, 12.7%)	0.65
Yes	13/593	2.6% (1.4%, 5%)		4/76	4.3% (1.4%, 12.8%)	—
Estrogen receptor status						

Predictor	Adjuvant Radiation Therapy			No Adjuvant Radiation Therapy		
	Events/Total	10-Yr Local	Regional Recurrence Rate	Events/Total	10-Yr Local	Regional Recurrence Rate
Positive	13/704	2.3% (1.2%, 4.2%)		8/145	5.6% (2.7%, 11.4%)	0.98
Negative	2/138	1.5% (0.4%, 5.7%)		1/19	5.9% (0.9%, 35%)	—
Margin width						
Free (≥ 2 mm)	31/1093	3.3% (2.2%, 4.9%)		14/278	5.4% (3.1%, 9.2%)	0.0006
Close (<2 mm)	2/100	4.8% (1.2%, 18.5%)		4/20	30.9% (12.4%, 64.6%)	—