Relationship Between Margin Width and Recurrence of Ductal Carcinoma In Situ

Analysis of 2996 Women Treated With Breast-conserving Surgery for 30 Years

Kimberly J. Van Zee, MS, MD, FACS, Preeti Subhedar, MD,* Cristina Olcese, BS,* Sujata Patil, PhD,† and Monica Morrow, MD, FACS**

Objective: Our goal was to investigate, in a large population of women with ductal carcinoma in situ (DCIS) and long follow-up, the relationship between margin width and recurrence, controlling for other characteristics.

Background: Although DCIS has minimal mortality, recurrence rates after breast-conserving surgery are significant, and half are invasive. Positive margins are associated with increased risk of local recurrence, but there is no consensus regarding optimal negative margin width.

Methods: We retrospectively reviewed a prospective database of DCIS patients undergoing breast-conserving surgery from 1978 to 2010. Univariate and Cox proportional hazard models were used to investigate the association between margin width and recurrence.

Results: In this review, 2996 cases were identified, of which 363 recurred. Median follow-up for women without recurrence was 75 months (range 0–30 years); 732 were studied for ≥10 years. Controlling for age, family history, presentation, nuclear grade, number of excisions, radiotherapy (RT), endocrine therapy, and year of surgery, margin width was significantly associated with recurrence in the entire population. Larger negative margins were associated with a lower hazard ratio compared with positive margins. An interaction between RT and margin width was significant ($P < 0.03$); the association of recurrence with margin width was significant in those without RT ($P < 0.0001$), but not in those with RT ($P = 0.95$).

Conclusions: In women not receiving RT, wider margins are significantly associated with a lower rate of recurrence. Obtaining wider negative margins may be important in reducing the risk of recurrence in women who choose not to undergo RT and may not be necessary in those who receive RT.

Keywords: breast-conserving surgery, ductal carcinoma in situ, margin width, radiotherapy

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Ductal carcinoma in situ (DCIS) now accounts for up to 21% of all breast cancers diagnosed in the United States each year.[1] Management options for DCIS range from mastectomy, to breast-conserving surgery (BCS) with adjuvant radiation therapy (RT), to BCS alone. Regardless of the type of local therapy, mortality as a result of DCIS is uncommon. However, local recurrence rates after BCS alone are high, ranging from 25 to 35% at 13 to 17 years of follow-up, and approximately half of all recurrences are invasive.[2–6] RT reduces the recurrence rate by approximately 50%, but does not reduce mortality[2–6] and can be associated with increased rates of cardiovascular disease and rare malignancies.[7–11] Tamoxifen also reduces recurrences among women whose DCIS expresses estrogen receptors, but, like RT, does not reduce mortality, and can result in elevated risk of uterine cancer and venous thromboembolic events.[3,12–14]

Although no subset of patients undergoing BCS for DCIS has been identified for which adjuvant RT does not reduce recurrence risk, there is interest in identifying those at lower risk of recurrence for whom adjuvant RT would result in a small absolute benefit. Numerous risk factors for recurrence have been identified, including age,[4–6,15,16] family history,[17–19] clinical presentation,[4,5,20] number of excisions,[16] nuclear grade and necrosis,[21–25] year of surgery,[16,26] and margin status.[4–6,16,20,24,27–29] Three prospective studies have successfully combined multiple factors to prospectively identify women at relatively low risk for recurrence after excision alone.[30–32] A nomogram that combines 10 different patient and pathological variables and adjuvant treatments to estimate risk of recurrence after BCS for DCIS allows identification of those at relatively low risk of recurrence[16] and has been validated in independent populations.[33–35]

However, of the various risk factors for recurrence of DCIS after BCS, the only characteristic that is potentially modifiable by the clinician is width of margin. Although multiple studies have shown that positive or close margins are associated with a higher risk of recurrence after BCS for DCIS, there is no consensus as to what constitutes an optimal negative margin width. We undertook this study to evaluate the association of margin width and local recurrence in women treated with and without RT for a 30-year time period at a single institution.

METHODS

After obtaining approval from the institutional review board, a prospectively maintained database was used to identify all patients undergoing definitive BCS for DCIS from 1978 to 2010 at Memorial Sloan Kettering Cancer Center. Patients with synchronous (n = 30) or metachronous (n = 29) bilateral DCIS were included once for each breast.

Clinical, pathological, and treatment variables included were age at diagnosis, menopausal status (pre- or perimenopausal vs postmenopausal), family history (at least one first- or second-degree family member with breast cancer), presentation (clinically palpable mass, nipple discharge, or Paget disease vs radiologic), nuclear grade [categorized as nonhigh-grade (including borderline cases focally reaching or approaching low grade DCIS, low grade, and intermediate grade) or high grade], number of excisions, margin width [categorized as positive (tumor on ink), close (≤2 mm), >2–10 mm (includes cases with margins described as widely clear), or >10 mm (includes patients with no residual disease in the reexcision

From the *Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; and the †Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY.

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Reprints: Kimberly J. Van Zee, MS, MD, FACS, Evelyn Lauder Breast Center, 300 E 66th St, New York, NY 10065. E-mail: vanzeek@mskcc.org.

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TABLE 1. Clinical and Pathologic Characteristics of Entire Population and by Receipt of Radiation

	Entire Population (N = 2996)		No Radiation (N = 1374)*		Radiation (N = 1588)*	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**
Age (yrs)						
≤50	845	28.2	350	25.5	486	30.6
>50	2151	71.8	1024	74.5	1102	69.4
Menopausal status						
Pre/peri	1038	34.6	442	32.1	586	36.9
Post	1946	65.0	924	67.2	999	62.9
Unknown	12	0.4	8	0.6	3	0.2
Family history						
No	1816	60.6	825	60.0	969	61.0
Yes	1136	37.9	515	37.5	610	38.4
Unknown	44	1.5	34	2.5	9	0.6
Presentation						
Clinical	386	12.9	195	14.2	178	11.2
Radiologic	2606	87.0	1176	85.6	1409	88.7
Unknown	4	0.1	3	0.2	1	<0.1
Nuclear grade						
Low/intermediate	1787	59.6	975	71.0	799	50.3
High	994	33.2	269	19.6	716	45.1
Unknown	215	7.2	130	9.5	73	4.6
Number of excisions						
1	1493	49.8	800	58.2	676	42.6
2	1282	42.8	525	38.2	745	46.9
≥3	217	7.2	47	3.4	165	10.4
Unknown	4	0.1	2	0.1	2	0.1
Margins						
Positive	104	3.5	43	3.1	59	3.7
Close (≤2 mm)	449	15.0	170	12.4	271	17.1
>2–10 mm	888	29.6	384	27.9	498	31.4
>10 mm	1347	45.0	669	48.7	672	42.3
Unknown	208	6.9	108	7.9	88	5.5
Radiation						
No	1374	45.9	1374	100.0	0.0	0.0
Yes	1588	53.0	0	0.0	1588	100.0
Unknown	34	1.1	0	0.0	0	0.0
Endocrine therapy						
No	2321	77.5	1152	83.8	1163	73.2
Yes	628	21.0	210	15.3	417	26.3
Unknown	47	1.6	12	0.9	8	0.5
Year of surgery						
1978–2000	1067	35.6	592	43.1	454	28.6
2001–2010	1929	64.4	782	56.9	1134	71.4

*Numbers do not sum to 2996 because of unknown receipt of radiation in 34 women.

specimen)], RT, endocrine therapy, and date of definitive surgery. Number of excisions was included because it is likely correlated with extent of DCIS and was previously shown to be statistically significantly associated with recurrence risk on multivariable analysis.[16] Postexcision mammogram was routinely performed for cases presenting as mammographic calcifications.

The outcome of interest was any recurrence, defined as ipsilateral breast recurrence of DCIS or invasive cancer, ipsilateral axillary nodal recurrence without ipsilateral breast recurrence, or, in 1 case, distant recurrence consistent with a breast primary carcinoma but without the presence of any ipsilateral recurrence or contralateral diagnosis of breast carcinoma. Time to event was defined as the interval between definitive surgery and date of first recurrence. Ten-year Kaplan-Meier recurrence estimates were calculated by margin width for the entire cohort and for the subsets with and without RT, and log-rank tests were used. A multivariable Cox model was created to evaluate the association of margin width with recurrence while controlling for other variables. Interaction between RT and margin width was assessed and separate models were created for the subsets with and without RT. Proportionality of hazards was checked for all Cox models and found to be appropriate. Statistical analysis was performed using SAS 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

From 1978 to 2010, 2996 cases were identified; the characteristics of the entire population and the cohorts with and without RT are presented in Table 1. Median age of entire population was 57 years (range 20–92 years). For those undergoing RT, median (range) age was 55 years (27–85 years) and for those without RT median age was 59 years (20–92 years). Recurrence occurred in 363, of which 159 were invasive (147 ipsilateral invasive breast recurrences, 2 ipsilateral axillary recurrences, and 10 simultaneous breast and axillary recurrences), 192 were DCIS, 11 were unknown type of breast recurrence, and 1 was distant metastasis without locoregional recurrence. Eighteen developed distant disease, of which 11 have died. Sixteen had ipsilateral invasive breast recurrence and 1 had ipsilateral DCIS breast recurrence before development of distant metastases.

Median follow-up for those without recurrence was 75 months (range 0–356 months). 732 women had at least 10 years of follow-up, and 615 of these had complete data. Overall, 336 women died, and 284 (9.5% of all women) died without having any recurrence.

Margin Width

Crude recurrence rates by margin width are shown in Table 2. Figure 1A shows Kaplan-Meier recurrence-free survival by margin width for the entire population, and 10-year recurrence rates are shown in Table 3. A trend toward lower risk of recurrence is associated with wider margins ($P = 0.087$). For women with positive margins, the 10-year rate of recurrence was 31%, as compared to 13% for women with >10 mm margins.

Margin Width and RT

We examined the effect of margin width on recurrence, stratified by use of RT; crude recurrence rates are shown in Table 2. Figure 1B and C shows Kaplan-Meier recurrence-free survival by margin width for those not receiving and those receiving RT; 10-year

TABLE 2. Crude Recurrences by Margin Width and Use of Radiation

	Entire Population (N = 2996)		No Radiation (N = 1374)*		Radiation (N = 1588)*	
Margin Width	**Events/ N**	**%**	**Events/ N**	**%**	**Events/ N**	**%**
Positive	16/104	15.4	10/43	23.3	6/59	10.2
Close (≤2 mm)	69/449	15.4	42/170	24.7	27/271	10.0
>2–10 mm	98/888	11.0	63/384	16.4	35/498	7.0
>10 mm	145/1347	10.8	87/669	13.0	58/672	8.6
Unknown	35/208	16.8	21/108	19.4	14/88	15.9

*Numbers do not sum to 2996 due to unknown receipt of radiation in 34 women.

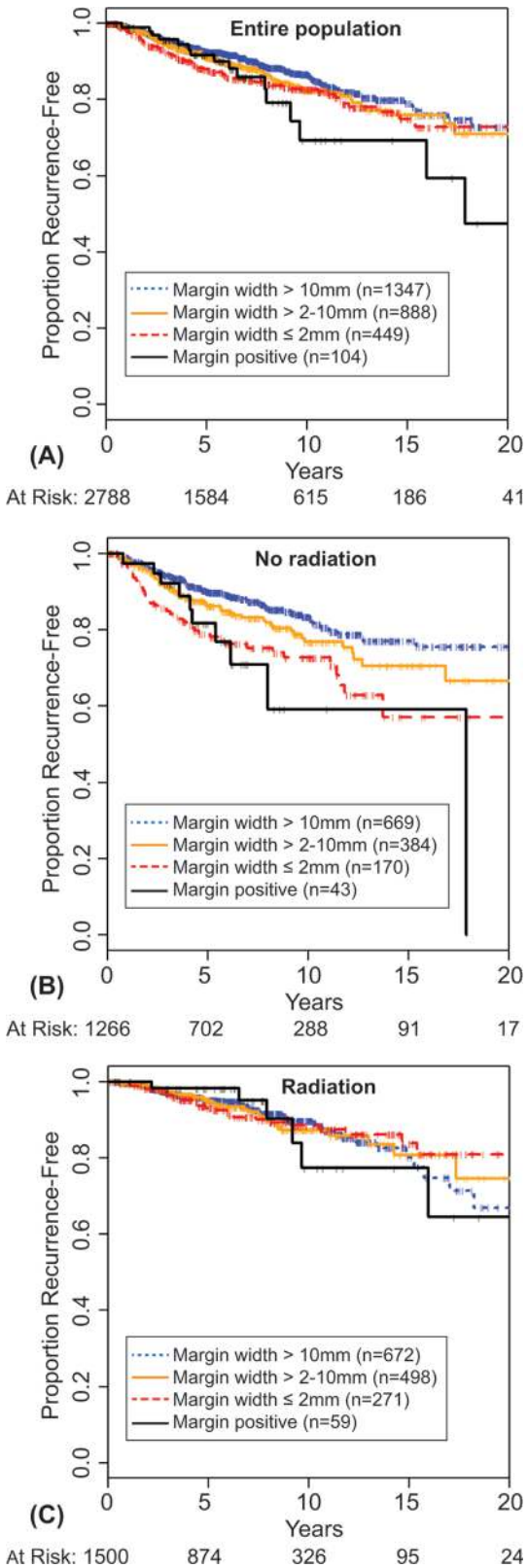

FIGURE 1. Proportion recurrence-free by margin width for (A) entire population, (B) no-radiation cohort, and (C) radiation cohort.

recurrence rates are shown in Table 3. Among those not receiving RT, the association of wider margins and lower recurrence was highly significant ($P = 0.0003$), whereas the association was not significant among those who received RT ($P = 0.99$).

For each margin width, the use of RT was associated with a statistically significant reduction in recurrence, with greater proportional and absolute risk reduction being associated with positive or close margins (Table 3, Fig. 2). This association remained significant after adjusting for 7 other variables.

Multivariable Analyses

Because numerous other factors are associated with recurrence, a multivariable model was built to control for factors that could affect the relationship of margin width and recurrence. Nuclear grade was not significant on either univariate ($P = 0.96$) or multivariable analysis ($P = 0.2$). Because its inclusion did not alter the results and because nuclear grade was unknown in 215 cases, it was not included in the final model. After controlling for age, family history, presentation, number of excisions, RT, endocrine therapy, and year of surgery (Table 4), wider margins were associated with lower risk of recurrence ($P = 0.0003$), with progressively lower hazard ratios associated with wider margins (0.78, 0.70, and 0.44 for negative margin widths of ≤ 2, >2–10, and >10 mm, respectively) as compared to positive margins.

Because of the apparent differential effect of margin width by RT (Figures 1 and 2, Table 3), an interaction term between margin width and RT was added to the multivariable model and was found to be significant ($P < 0.03$). To explore this relationship further, a multivariable model was fit to the subsets of patients not receiving and receiving RT (Table 5). This confirmed that there is a differential effect of margin width by RT. In those not receiving RT, the relationship between wider margins and lower rates of recurrence was even stronger [hazard ratio (HR) = 0.75, 0.58, 0.31 for negative margin widths of ≤ 2, >2–10, >10 mm, respectively, as compared to positive, $P < 0.0001$], whereas for those receiving RT, there was no clear relationship ($P = 0.95$).

To further explore various margin width thresholds among those receiving RT, we created multivariable models with margin width dichotomized into positive versus tumor not on ink, ≤ 2 vs >2 mm, and ≤ 10 vs >10 mm, but found no significant difference ($P = 0.67$, $P = 0.96$, $P = 0.70$, respectively) in risk of recurrence with any threshold.

DISCUSSION

The overview of the 4 prospective randomized trials of RT for DCIS found that negative margins are associated with a lower risk of recurrence.[2] However, because margin status was dichotomized as positive versus negative,[4,6] or within 1 mm versus over 1 mm,[5,24] the optimal negative margin width cannot be assessed in those studies. However, Pinder et al examined a subset of 637 cases from the 1701 cases in the UK/ANZ trial for whom actual margin width was available.[24] They found that the HR for risk of recurrence was halved in cases with ≥ 5 mm margins as compared to those with <1 mm margins (HR = 0.46, $P = 0.03$); they did not report the number that received RT or tamoxifen, nor did they stratify by adjuvant treatment.

Several retrospective analyses have been undertaken in an attempt to address the relationship of margin width and recurrence of DCIS. Silverstein et al[21] first included margin width as one of 3 predictors of local recurrence (along with tumor size and nuclear grade/necrosis classification) in his Van Nuys Prognostic Index. In a population of 333 women with a median follow-up of 79 months, larger margin widths were associated with lower risk of recurrence [$P < 0.04$, margin widths were categorized as wide (≥ 10 mm), intermediate (1–9 mm), and close (<1 mm)]. Silverstein et al[27] later

TABLE 3. Ten-year Recurrence Rates by Margin Width and by Receipt of Radiation

Margin Width	Entire Population With Known Margin Width (N = 2788)*	No Radiation (N = 1266)†	Radiation (N = 1500)†	HR‡ for Radiation	*P*§ for Radiation	Adjusted HR for Radiation¶	*P*‖ for Radiation
Positive	31	41	23	0.22	0.0026	0.10	0.0036
Close (≤2 mm)	17	27	12	0.32	<0.0001	0.29	<0.0001
>2–10 mm	18	23	13	0.46	0.0002	0.42	0.0006
>10 mm	13	16	10	0.66	0.0132	0.54	0.0013
P# for margin width	=0.087	=0.0003	=0.99				

*In entire population of 2996, 208 patients had unknown margin width.
†Numbers do not sum to 2788 because 22 patients with known margin width had unknown radiation status.
‡HR of radiation versus no radiation.
§Log rank test for effect of radiation.
¶HR of radiation versus no radiation, controlling for age, family history, presentation, nuclear grade, number of excisions, endocrine therapy, year of surgery.
‖*P* value for effect of radiation in Cox model, controlling for age, family history, presentation, nuclear grade, number of excisions, endocrine therapy, year of surgery.
#*P* value of log-rank test for difference in recurrence by margin width.
HR indicates hazard ratio.

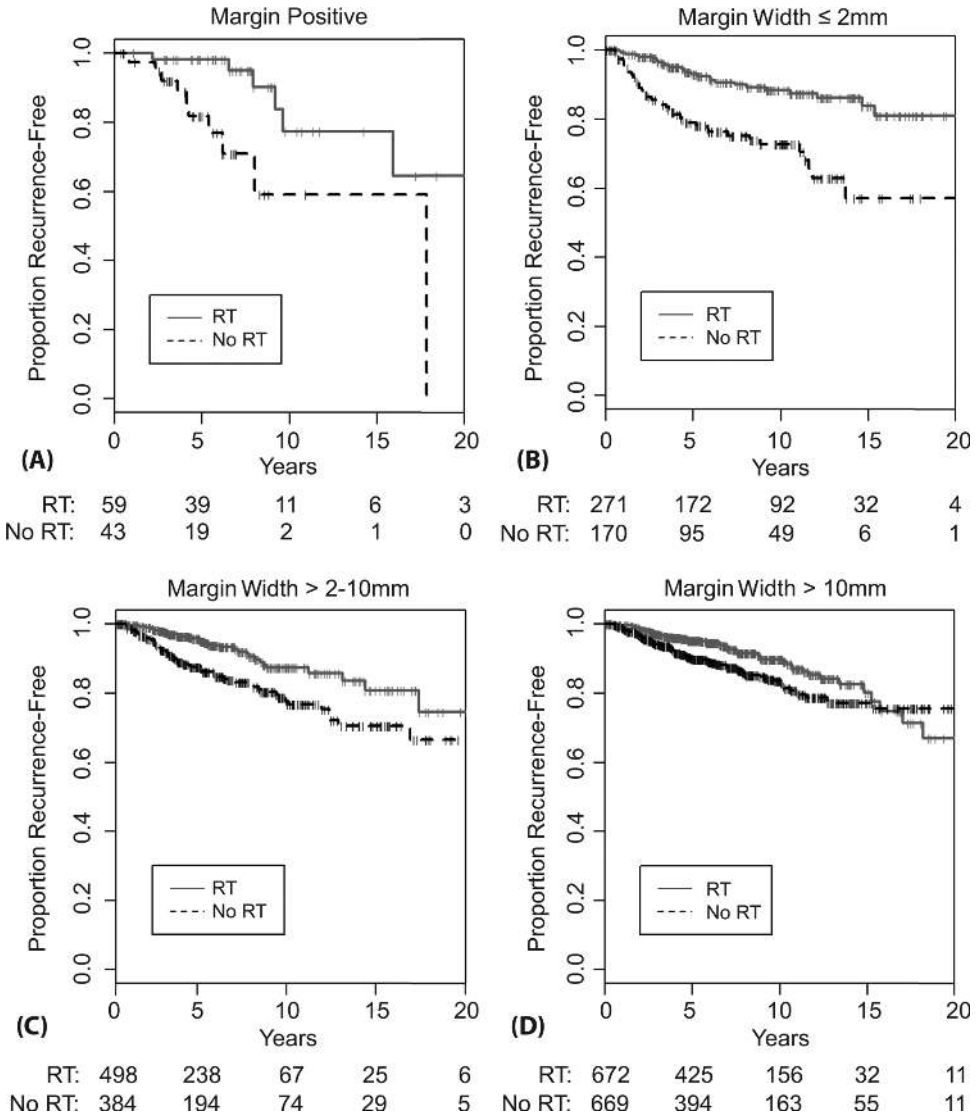

FIGURE 2. Proportion recurrence-free by use of radiation for (A) positive margins, (B) margin width ≤2 mm, (C) margin width >2–10 mm, and (D) margin width >10 mm.

TABLE 4. Multivariable Cox Regression Analysis of the Association of Margin Width and Recurrence in 2708* Women With DCIS Treated With Breast-conserving Surgery, Controlling for Other Factors

Variable	N	Events	HR	*P*
Age				
Per year			0.978	<0.0001
Family history				
No	1662	187	1	0.03
Yes	1046	138	1.28	
Presentation				
Radiologic	2394	264	1	0.03
Clinical	314	61	1.38	
Number of excisions				
1	1300	138	1	0.006
2	1204	155	1.27	
≥3	204	32	1.96	
Radiation				
No	1225	201	1	<0.0001
Yes	1483	124	0.44	
Endocrine therapy				
No	2110	285	1	<0.0001
Yes	598	40	0.48	
Year of surgery				
1978–2000	826	188	1.47	0.002
2001–2010	1882	137	1	
Margin width				
Positive	98	16	1	0.0003
Close (≤2 mm)	435	69	0.78	
>2–10 mm	861	97	0.70	
>10 mm	1314	143	0.44	

*In entire population of 2996, 288 cases had at least one missing data point, resulting in population for multivariable analysis of 2708.
HR, hazard ratio.

reported that among a population of 469 with a median follow-up of 81 months, 8-year recurrence rates for those not receiving RT were 3%, 20%, and 58% for those with wide, intermediate, and close margins, respectively, as compared to 4%, 12%, and 30% for those receiving RT. They concluded that there was no significant benefit of RT in patients with wide margins.

Solin et al[36] reported that in a multivariable analysis of 1003 women with mammographically detected DCIS treated with BCS and RT, and median follow-up of 8.5 years, margin status and age were the only statistically significant factors associated with recurrence. Compared with negative margins, positive margins (tumor on ink) had a HR of 3.35 ($P = 0.00035$) and close margins (defined as <2, ≤ 2, <2–3, or <3 mm) had a HR of 1.9 ($P = 0.03$).

In a retrospective study of 460 women treated with BCS without RT and referred to the British Columbia Cancer Agency from 1985 to 1999, Wai et al[37] reported that 10-year local recurrence rates were lower with negative margins (9%) as compared to close (17%), positive (31%), or unknown (32%) margins ($P < 0.0001$).

A review of the role of margin status on recurrence in DCIS patients after BCS and RT included 7 publications for which a comparison between negative and close (variably defined as <1 to <5 mm) margins could be made. The odds ratio for local recurrence with negative margins as compared to close was 0.59 ($P < 0.001$).[38] In the subset of studies for which a specific margin width could be determined, analysis showed that 2 mm margins were associated with lower risk than <2 mm (5.8% vs 10.4% local recurrences, OR (odds ratio) = 0.53, $P < 0.05$), and associated with a nonsignificantly higher risk than 5 mm margins (5.8% vs 3.9% local recurrences, OR 1.51, $P > 0.05$).

Wang et al[39] performed a network metaanalysis of the association of specific margin thresholds and recurrence for women with DCIS treated with or without RT after BCS. The authors used a variety of complex statistical methods, including both frequentist

TABLE 5. Multivariable Cox Regression Analysis of Recurrence, Stratified by Use of Radiation

	No Radiation (N = 1225)*				Radiation (N = 1483)*			
Variable	N	Events	HR	*P*	N	Events	HR	*P*
Age at surgery								
Per year			0.987	0.02			0.956	<0.0001
Family history								
No	753	114	1	0.05	909	73	1	0.23
Yes	472	87	1.32		574	51	1.25	
Presentation								
Radiologic	1068	162	1	0.06	1326	102	1	0.43
Clinical	157	39	1.4		157	22	1.22	
Number of excisions								
1	688	100	1	0.0003	612	38	1	0.66
2	492	85	1.37		712	70	1.18	
≥3	45	16	3.18		159	16	1.30	
Endocrine therapy								
No	1026	180	1	0.003	1084	105	1	0.002
Yes	199	21	0.50		399	19	0.46	
Year of surgery								
1978–2000	459	123	1.60	0.003	367	65	1.18	0.44
2001–2010	766	78	1		1116	59	1	
Margin width								
Positive	40	10	1	<0.0001	58	6	1	0.95
Close (≤2 mm)	167	42	0.75		268	27	0.95	
>2–10 mm	369	62	0.58		492	35	1.00	
>10 mm	649	87	0.31		665	56	0.88	

*In entire population of 2996, 288 cases had at least one missing data point, resulting in population for multivariable analysis of 2708.

and Bayesian approaches. Their analyses showed that a negative margin threshold of 10 mm was associated with a lower recurrence than a threshold of 2 mm ($P < 0.001$), regardless of use of RT. Because the analysis pooled many different studies, it could not adjust for the many other factors known to be associated with local recurrence.

Here, in this large cohort of well-characterized cases of DCIS treated with BCS, we have found a strong association of margin width and risk of recurrence in those not receiving RT, but not in those receiving RT. Our finding is unique because our population was large (n = 2996) with substantial follow-up (615 with complete data were followed for at least 10 years), numerous patient, pathologic and treatment characteristics were known for each case, and the large size and long follow-up allowed the statistical power to control for numerous factors that are known to be associated with local recurrence. Furthermore, we were able to examine the association of margin width and local recurrence separately for those that did and did not receive RT, which revealed a differential effect.

Among women not receiving RT, the width of negative margin was strongly related to risk of recurrence, likely because a wider negative margin is associated with a lower volume of residual disease. However, among women receiving RT, there was no significant association. In an earlier report, we examined the 10-year recurrence rates of a subset (n = 291) of the population in the current analysis. These women had DCIS treated with BCS from 1991 to 1995 and were studied for a median of 11 years.[20] Most cases (93%) had pathology review by a breast pathologist. We found lower 10-year recurrence rates with ≥10 mm margins (21%) as compared to 1 to 9 mm margins (27%) or <1 mm margins (42%) among those not receiving RT, but not among those receiving RT (13%, 12%, and 11%, respectively). The current much larger analysis confirms this finding of a differential effect of margin width depending on the use of RT.

This finding of a differential association of margin width and local recurrence, depending on the use of RT, demonstrates the complexity of understanding risk factors for recurrence for DCIS. In their most recent update of NSABP B-24, Wapnir et al[4] reported a differential association of margin status and local recurrence, depending on the use of tamoxifen. In women receiving both RT and tamoxifen, margin status (involved/uncertain vs free) was not significantly associated with recurrence, whereas for those receiving RT alone, it was highly significant (HR 2.61, $P < 0.001$ for invasive recurrence; HR 1.65, $P = 0.05$ for DCIS). The interaction between use of tamoxifen and margin status was significant ($P = 0.04$). The observation that the association of margin status or margin width with recurrence rate is affected by use of adjuvant therapy is consistent with the idea that margin status and margin width are predictors of risk of or volume of residual disease in the breast. In those who do not receive effective adjuvant treatment, margin width is highly correlated with risk of recurrence. In those who receive effective adjuvant treatment, it can eradicate the residual disease, thereby lessening the association with margin width.

A limitation of our series is that very few women had positive margins, as it is our standard practice to achieve clear margins. Most positive margins were at the dermis or the pectoralis fascia, rather than at a radial margin. Furthermore, cases with positive or close margins generally had very limited, focal disease at or near the inked margin. Together, these observations suggest that our patients with close or positive margins likely had a lower residual disease burden than some other series. This limitation may cause our reported recurrence rates for close and positive margins to underestimate recurrence rates for women with a greater volume of disease at or near the margin, as it is known that volume of disease near the margin is related to recurrence.[20,40]

In contrast to the findings of Dunne et al,[38] among women receiving RT we could find no significant difference in recurrence by any categorization of margin width, including ≤2 versus >2 mm. This is likely because of the limited amount of disease near the margin in our patients with close or positive margins. Similarly, in contrast to Wang et al,[39] we could find no significant difference in recurrence between margin widths of ≤10 and >10 mm among those receiving RT. This difference in findings may be because of our ability to control for numerous other factors in our multivariable model.

CONCLUSIONS

In a large, well-characterized population of women with DCIS, where numerous factors were controlled for, we have found that margin width is strongly associated with risk of recurrence for women undergoing BCS who do not receive RT. In contrast, we found no association among those who do receive RT, demonstrating a differential association of margin width and recurrence, depending on adjuvant treatment. These results support the conclusion that obtaining wider negative margins may be important in reducing the risk of recurrence in women who choose not to undergo RT, and may not be necessary in those who receive RT.

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DISCUSSANTS

W.C. Wood (Atlanta, GA):

I first have a disclosure. I have chaired advisory board meetings for Genomic Health for the DCIS score.

We have heard the report of 2 large populations of women with DCIS, 1 with excision and no radiation and one with. Many in each group also received hormone therapy. If their intent were to compare the 2 groups to address the effects of radiation, I would protest vigorously that any differences simply reflected differences between the populations, but instead they present the effect of margin size on recurrence, finding none in the irradiated population but a clear effect in the nonirradiated women.

A positive margin cutting through the lesion, leaving an unknown volume behind, of course, had the highest recurrence risk. The risk at 10 years fell from 27% if the margin was <2 mm to 23% if it was between 2 and 10 mm to 16% if it was greater than a centimeter. Now, I must admit that a reduction from 27% to 23% at 10 years does not overwhelm me.

Roland Holland and others subsequently found foci of ductal carcinoma in situ >2 cm away in 30% of mastectomies that they studied for extension of DCIS. So a few millimeters more clearly does not mean we got it all. I suspect that when the surgeon thought she had a clear margin, but the pathologist finds extending DCIS close to the margin, we are seeing different biologies behaving. I expect that genomic assays will prove better than margin width at identifying women at low risk of recurrence without radiation in the future.

I have 2 questions.

First, you analyzed nine variables. Why not the size of the lesion? A 2-mm margin may have different significance in a 1-cm focus of DCIS than in a 3-cm focus. We found that in the early breast cancer trials collaborative group analysis of 3723 women who were randomized to radiation or none if the tumor was <2 cm in diameter, the local failure rate at 10 years was 29%. If it was >2 cm, it was 39% at 10 years.

My second question is, for any surgeons in the audience who do breast surgery, what does your study lead you to do for your patient with a 1-mm clear margin or a 3-mm clear margin for that?

We know from our overview of randomized trials—and you pointed it out—that adding radiation reduces risk of recurrence but has enough offsetting harms that it has no effect at all on survival. Should we re-excise these women with close margins? They would suffer greater cosmetic loss. You found increasing recurrence with repeat excisions, again suggesting that biology was at work and not surgical insufficiency. Should we add radiation for close margins?

Irradiating 100 such women would produce 30 to 40 women who, at the end of 5 years, would rate their breasts as fair to poor cosmetically in the best-randomized trials. The 10 women who have a recurrence despite having had radiation would be told that they need a mastectomy because they have already had their radiation. We will not even consider the fiscal costs of irradiating all these women.

What have you taken away from your study for your patient with close margins?

This is a superb addition to our knowledge about DCIS. There is much more material in the manuscript than you were able to present here, and I strongly recommend the manuscript to our colleagues.

Response From K.J. Van Zee:

To address your first question about size, size was not available on our pathology reports, which is where the data came from for a significant proportion of our patients. Therefore, to include size would mean our N would go way down.

Why is size not commonly reported with DCIS? It is a microscopic disease; there is no gross correlate. The pathologists have difficulty giving a size. Often they see skip lesions. There are a million reasons why pathologists say it is difficult to give sizes. In the current modern day, sizes are given routinely on pathology reports, but in the 1980s and 1990s, we did not routinely have size reported. I just want to point out that even in the overview of the four prospective randomized trials, size was missing in a majority of the patients, even in those prospective trials.

In terms of what to do, what do we take away from this? Well, I think, as shown in the multivariable models, there are multiple different factors related to local recurrence, and it is not just one. Margin width is just one factor. I think the decision making regarding the different options for a woman with DCIS range all the way from mastectomy, or even bilateral mastectomy these days, to lumpectomy with radiation to lumpectomy alone, which is an awfully broad assortment of choices.

I think one of the most time-consuming things I do in the office is to discuss the pros and cons of those different options. You may be aware also of a nomogram that we created a few years ago that incorporates all these numerous variables. With the online DCIS nomogram, you can get a rough recurrence risk estimate with or without radiation, with or without tamoxifen, and, with these different variables, that can help in making that decision. It often is a lower risk than one would think, because of the improved recurrence rates in more recent years as compared to those reported in the randomized trials. The DCIS nomogram has now been validated by several different groups.

P. Borgen (Brooklyn, NY):

I have 2 disclosures. As with Dr. Wood, I have a consulting agreement with Genomic Health, although I do not have an equity position in that company. My second disclosure is I feel like a proud parent standing here. It was 21 years ago that we started working together, and I am very proud of you and how much you have taught us about DCIS.

Our mutual mentor, Dr. Murray Brennan, now Sir Murray Brennan, had a favorite aphorism that was ''biology beats technique.'' That truism takes on a potentially different meaning when we think about DCIS. A growing wealth of information suggests that there is a reservoir of DCIS that is either highly unlikely to ever progress to invasive cancer, or may do so at such a slow rate as to not be clinically significant. Your data actually further confirms this. You showed us in your table in the paper that in nonirradiated patients with very, very small margins, less than 2 millimeters, >60% were alive, free of disease, 20 years later.

My question is a continuation of what Dr. Wood alluded to. Is the next step in refining our approach to DCIS better class prediction using, for example, genomic profiling? Would you consider having the archival material from your patient's profile? Does material exist?

Response From K.J. Van Zee:

I would love to do a study combining and comparing the DCIS score and a combination of multiple different clinical variables that are available to all of us. I think they are highly correlated. But they are also probably additive, meaning that they would complement one another. However, you can get a pretty good area under the ROC curve with clinical variables alone that is similar to that of the Oncotype for invasive cancer. The area under the ROC curve is approximately 0.69 for the regular Oncotype Recurrence Score for invasive cancer and that for the DCIS nomogram is about the same, suggesting that the DCIS nomogram has similar discrimination as the regular Oncotype Recurrence Score for invasive cancer.

I would love to do the study. However, it is very difficult to get the archival material and it would be very expensive. But sure, send me the funding.

A. Giuliano (Los Angeles, CA):

I have no disclosures.

First, I would like to point out the importance of this paper. It supports the randomized trials that radiation decreases recurrence, but more importantly it shows that with radiation, there is no diminution of recurrence with obtaining wider margins. Therefore, we surgeons should limit our desire to reoperate on patients who have close margins. No tumor on ink is probably adequate. These women do not need multiple reoperations. I think it is a very important paper, and I applaud you for it.

I do have some questions, however.

First, how did you measure margins? Many of us remove the tumor and then take separate margins, especially if the tumor comes out in fragments. What is your protocol to measure margins?

Second, when you are out 10 and 15 years, are these local recurrences or are they new tumors? Did you attempt to look at the tumor location and define a local recurrence as opposed to a new carcinoma in a woman at increased risk for breast cancer?

Third, with the randomized trials showing the value of radiation, I was surprised that half of the patients at Memorial did not get radiation. Is that Dr. Brennan's influence?

Response From K.J. Van Zee:

Probably.

To address your first question, what is the protocol for measuring margins? Well, all margins are inked and the pathologist measures the distance from the closest margin. That is the short answer. Through the years, there have been different protocols used for assessing margins. Currently, we do an excision and then a separate margin excision for each direction in the operating room and send each margin separately. That procedure began after this series ended, so that was not included in this series.

In terms of local recurrence versus a new cancer, any ipsilateral breast tumor recurrence was called a recurrence for the purposes of this study, regardless of whether it was the same quadrant or a different quadrant.

You can see from the Kaplan-Meier curves going out all the way, 20 and even 30 years, that there seems to be a constant hazard ratio over time. They do not all happen early on and then plateau. It seems to be constant. I am sure some of those are new primaries, but i also think some of the low-grade DCISs, probably with low Oncotype scores, take a long time to recur.

S. Klimberg (Little Rock, AR):

I'm very conflicted but I have no relevant conflicts.

Recently, the SSO in ASTRO published a consensus guideline with the input of multiple and national societies on invasive ductal

cancers, stating no tumor on ink. However, we did not address DCIS, as you pointed out, in that there is been a lack of consensus regarding the appropriate margin width for these patients for breast conservation.

Dr. Van Zee and colleagues provide us with information on the outcomes of patients with DCIS treated for 30 years at their institution. The paper is an important contribution to the literature, as it's a large experience from a single institution with dedicated specialists in breast and diagnosis and treatment throughout all specialties.

Specifically, Dr. Van Zee has spent 20 years updating, maintaining, and cleaning up this database, which makes it a tremendous resource to answer some of the questions about DCIS. Particularly, she has a Masters degree in statistics, so she has done this very well.

My questions are, can you elaborate on the institutional changes in practice in regard to DCIS and margin assessment over the last 20 years that you have developed and updated this database? Specifically, I think you have already answered how you assess margins, but I think you've changed how you assess margins as well.

How are patients selected for radiation? Is it an individual basis, a provider decision, or is there an institutional algorithm that factor in clinical and pathological variables?

Since we know from randomized trials that patients with younger age tend to have higher risk of local failure over time, does age impact on your decision making in that regard?

When do you do partial versus whole breast? Because you really didn't go into that here or in your manuscript, and I am not sure that you have that data. Do you?

As you know, Julie Margenthaler and I published a paper on margin index, which is millimeters of margin over millimeters of tumor for invasive breast cancer with an ROC curve, under the curve is 0.9, that showed you need a bigger margin the bigger the lesion is to remove the residual tumor. Surgeons do that instinctively because if I see a bigger tumor, I am going to go wider. If it's a little bitty thing, I am not going to take as much. I suspect some of the respective papers on margin for invasive breast cancer are really all over the place because of that fact. If we went back and looked at margin index, it would be a different story.

The database we were using didn't really have a big enough one for DCIS to develop a margin index. On those patients where you did measure size, can you go back and do something with margin index to look at that? Because that really might obviate the need for radiation in a larger number of patients and explain some of the recurrences. Did you see a decrease in size of DCIS over time due to the relevancy of screening?

Response From K.J. Van Zee:

Margin assessment methods, as I have said, clearly changed over time. Back in the 1970s, inked margins were not routine, for example. Through the years, we have tried some different methods, including tangential shaving of the specimen by the pathologist, reexcision of the specimen cavity by the surgeons, perpendicular margins. We have tried different methods. The way we are doing it now clearly achieves the lowest rate of reexcision and the lowest rate of positive margins, probably at a cost of taking a little bit more tissue.

Patient selection. We do not have a hard and fast institutional algorithm. The default is always to consider radiation and refer for radiation oncology consult, but, as I said, it is a difficult conversation and discussion weighing the pros and cons. There are a lot of women that really are reluctant to undergo radiation, especially since there is no survival benefit.

We do weigh the multiple different factors involved and try to align a patient's risk and her goals in terms of risk reduction versus cosmesis versus doing radiation, et cetera, in trying to choose the optimal treatment for each individual patient.

Age. Clearly, age is an important risk factor in terms of local recurrence. For someone who is very young, one is reluctant to not radiate them because you know their risk is high. On the other hand, if there is someone who is going to be more hurt by radiation, it is probably a younger person who has a longer life ahead of them.

Partial versus whole breast radiation. For the most part, all of these women had whole breast radiation. We only have been doing routine partial breast radiation as part of the prospective national trials, so there are few women that had partial breast radiation.

Your comments about margin index are very intriguing. I think you are absolutely right. We all intuitively, for a larger extent of disease, take wider margins in a higher volume. Our number of excisions in some ways is related to extent of disease for that reason.