VOLUME 30 · NUMBER 6 · FEBRUARY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Evaluation of a Breast Cancer Nomogram for Predicting Risk of Ipsilateral Breast Tumor Recurrences in Patients With Ductal Carcinoma in Situ After Local Excision

Min Yi, Funda Meric-Bernstam, Henry M. Kuerer, Elizabeth A. Mittendorf, Isabelle Bedrosian, Anthony Lucci, Rosa F. Hwang, Jaime R. Crow, Sheng Luo, and Kelly K. Hunt

See accompanying editorial on page 577

Min Yi, Funda Meric-Bernstam, Henry M. Kuerer, Elizabeth A. Mittendorf, Isabelle Bedrosian, Anthony Lucci, Rosa F. Hwang, Jaime R. Crow, Kelly K. Hunt, The University of Texas MD Anderson Cancer Center; Sheng Luo, The University of Texas Health Science Center at Houston, Houston, TX.

Submitted April 15, 2011; accepted October 7, 2011; published online ahead of print at www.jco.org on January 17, 2012.

Supported in part by the National Institutes of Health support grant No. CA016672 to the MD Anderson Cancer Center.

Presented in part at the 33rd Annual San Antonio Breast Cancer Symposium, December 8-12, 2010, San Antonio, TX.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Kelly K. Hunt, MD, Department of Surgical Oncology, Unit 1484, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Houston, TX 77030; e-mail: khunt@mdanderson.org.

0732-183X/12/3006-600/$20.00

DOI: 10.1200/JCO.2011.36.4976

ABSTRACT

Purpose
Prediction of patients at highest risk for ipsilateral breast tumor recurrence (IBTR) after local excision of ductal carcinoma in situ (DCIS) remains a clinical concern. The aim of our study was to evaluate a published nomogram from Memorial Sloan-Kettering Cancer Center to predict for risk of IBTR in patients with DCIS from our institution.

Patients and Methods
We retrospectively identified 794 patients with a diagnosis of DCIS who had undergone local excision from 1990 through 2007 at the MD Anderson Cancer Center (MDACC). Clinicopathologic factors and the performance of the Memorial Sloan-Kettering Cancer Center nomogram for prediction of IBTR were assessed for 734 patients who had complete data.

Results
There was a marked difference with respect to tumor grade, prevalence of necrosis, initial presentation, final margins, and receipt of endocrine therapy between the two cohorts. The biggest difference was that more patients received radiation in the MDACC cohort (75% at MDACC *v* 49% at MSKCC; $P < .001$). Follow-up time in the MDACC cohort was longer than in the MSKCC cohort (median 7.1 years *v* 5.6 years), and the recurrence rate was lower in the MDACC cohort (7.9% *v* 11%). The median 5-year probability of recurrence was 5%, and the median 10-year probability of recurrence was 7%. The nomogram for prediction of 5- and 10-year IBTR probabilities demonstrated imperfect calibration and discrimination, with a concordance index of 0.63.

Conclusion
Predictive models for IBTR in patients with DCIS who were treated with local excision are imperfect. Our current ability to accurately predict recurrence on the basis of clinical parameters alone is limited.

J Clin Oncol 30:600-607. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Breast-conserving therapy has become the most common treatment for patients with ductal carcinoma in situ (DCIS) in the United States.[1] Both mastectomy and local excision with radiation therapy (RT) have been shown to be effective therapeutic approaches for the local management of patients with DCIS.[2] A randomized, controlled trial comparing mastectomy with local excision and RT has not been performed, but current data demonstrate similar long-term survival times with either approach. Mastectomy can reduce the risk of local treatment failure to as low as 1% to 2% at 5 years. Local excision with postoperative RT has been associated with local treatment failure rates of approximately 5% to 10% at 5 years[3]; however, despite this higher treatment failure rate, many clinicians and patients prefer breast conservation, because there is no difference in long-term survival.

An international survey of more than 1,000 physicians who treat breast cancer revealed marked differences in opinions and practice patterns in the management of DCIS.[4] Four large, prospective, randomized trials have all shown a highly significant reduction in the incidence of ipsilateral breast tumor recurrence (IBTR), ranging from 47% to 67%, with the administration of RT after local excision.[3,5-8] However, the need to commit all patients to RT is controversial, and some physicians are less likely to recommend RT[4] or tamoxifen treatment[9] for patients with DCIS.

Recently, investigators at the Memorial Sloan-Kettering Cancer Center (MSKCC) identified 10 independent predictors of IBTR in patients with DCIS by multivariate analysis: age at diagnosis, family history of breast cancer, presentation (clinical *v* radiologic), adjuvant radiation therapy, adjuvant endocrine therapy, nuclear grade, necrosis, surgical margins, number of surgical excisions, and year of surgery.[10] These predictors were combined in a nomogram to identify the individual risk of a patient who had DCIS for recurrence after local excision. The output of the nomogram is the predicted probability of recurrence at 5 and 10 years and can be calculated via the MSKCC Web site (http://www.mskcc.org/applications/nomograms/breast/DuctalCarcinomaInSituRecurrencePage.aspx). The nomogram was based on a data set from 1,681 patients and was internally validated by using 200 bootstrap samples.[10] It has not been validated by the MSKCC investigators in an independent cohort or externally validated by other institutions. The aim of our study was to evaluate the nomogram by using a large, external, and independent cancer center database.

PATIENTS AND METHODS

Patient Selection and Data Collection

Patients with a final diagnosis of DCIS who underwent local excision from January 1990 through December 2007 were indentified from our database. Patients with follow-up time less than 1 year were excluded. The MD Anderson Cancer Center (MDACC) institutional review board approved this study. We extracted demographic, pathologic, clinical, and follow-up data. Age was recorded as a continuous variable. Family history of breast cancer was considered positive if either first- or second-degree relatives had diagnoses of breast cancer. Nuclear grade was defined as low or intermediate/high. Necrosis was defined as present or absent. Margin width was classified as positive, close (< 2 mm), or negative; if re-excision was performed, the margin was scored as negative if there was no residual disease in the re-excision specimen. Presentation was classified as clinical (DCIS detected by palpable mass or nipple discharge) or radiologic (DCIS detected through routine imaging). All the MSKCC variables with definition are included in our study except variable-time period of treatment and variable-architecture. Variable-time period of treatment was dichotomized into two 9-year (*v* 8-year for MSKCC data) intervals (ie, 1990 to 1998 and 1999 to 2007). Variable-architecture is not included in this study, as it is only used to describe the data and is not a variable in the MSKCC nomogram. An IBTR was defined as the development of invasive cancer or DCIS histology in the treated breast. Time to IBTR was the interval from surgery to date of IBTR diagnosis.

Treatment

Standard treatment for patients with DCIS after local excision is RT in our center. However, patients with small, low-grade tumors that have wide margins of excision can choose to avoid RT. Some patients may decline RT regardless of the clinical recommendation.

Since the report of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 study,[11] patients with DCIS in our center have been offered endocrine therapy in the postoperative setting if there were no contraindications. This practice changed in 2002, when a reanalysis of NSABP B-24 found that the benefit of tamoxifen is greatest in patients who have estrogen receptor (ER) –positive DCIS.[12] We now recommend endocrine therapy only to patients with ER-positive DCIS.

Statistical Analysis

Patient, tumor, and treatment characteristics were evaluated. Kaplan-Meier survival curves were calculated, and the log-rank test was used to compare the IBTR-free survival between groups. We also used cumulative incidence estimates, because, when competing risks are present, the Kaplan-Meier method overestimates the true failure probability.[13] Patients who had not had recurrence at the time of analysis or who died without recurrence were censored at last follow-up. A multivariate Cox proportional hazards model was used to identify significant factors associated with IBTR without violation of the proportional hazards assumption.

The predicted 5- and 10-year probabilities of recurrence were calculated for each patient with the nomogram available on the MSKCC Web site. A receiver operating characteristic (ROC) curve was drawn, and the areas under the curve (AUCs) at the 5- and 10-year follow-up evaluations were calculated to assess the discriminative power of the nomogram. It is generally accepted that AUC values of 0.7 to 0.8 represent reasonable discrimination, whereas AUC values exceeding 0.8 represent good discrimination.[14] We also assessed the discriminative ability of the nomogram by using the Harrell concordance index (C index), a widely applicable measure of predictive discrimination—one that applies to ordinary continuous outcomes, dichotomous diagnostic outcomes, ordinal outcomes, and censored time-until-event response variables.[15,16] Similar to the AUC, the C-index can range from perfect concordance (1.0) to random predictions (0.5).[14,17]

Calibration of the nomogram was assessed by plotting the observed IBTR rate (the mean Kaplan-Meier estimate for patients in each octile) against the nomogram 5- and 10-year predicted IBTR probability (ie, the mean nomogram predicted probability for patients in each octile). A perfectly accurate nomogram prediction model would result in a plot in which the observed and predicted probabilities for given groups would fall along the 45-degree line. The distance between the pairs and the 45-degree line is a measure of the absolute error of the nomogram's prediction.[18] All statistical analyses were performed by using R 2.10.1 (http://www.r-project.org/). All *P* values were two tailed, and $P \leq .05$ was considered significant.

RESULTS

Patient, Tumor, and Treatment Characteristics

There were 794 patients in this study. Table 1 lists the comparisons between the MDACC and MSKCC cohorts, including patient demographics, disease characteristics, and treatment variables. Missing frequencies are listed when applicable. Overall, in the MDACC cohort, patients were more likely to be treated with radiation if the DCIS was high nuclear grade (42.5% *v* 10% of patients with low nuclear grade; $P < .001$) or had necrosis (67.5% *v* 32.5% of patients without necrosis; $P < .001$). More patients received radiation after 2000 (75.4% *v* 66.8% of patients had radiation before 2000; $P = .01$). The 218 patients treated without radiation were more likely to have smaller tumors (mean, 1.0 cm; median, 0.7 cm; *v* mean, 1.5 cm; median, 1 cm in the radiation group; $P < .001$) and lower-grade tumors (78.5% grades 1 to 2 tumors *v* 57.5% grades 1 to 2 tumors in the radiation group; $P < .001$). More patients received endocrine therapy after 2000 (41.9% *v* 12.6% of patients had endocrine therapy before 2000; $P < .001$). Eighteen patients used tamoxifen before surgery for the treatment of a contralateral breast cancer; 24 patients had mammographically occult DCIS detected by MRI or ultrasound examination.

IBTRs

The median follow-up time was 7.1 years for all patients. There were 572 (72.0%) patients with at least 5 years follow-up time and 206 (25.9%) that had at least 10 years follow-up time. Among the 794 patients, 63 (7.9%) developed IBTR. Fifty-seven percent of IBTRs were invasive (with or without DCIS), and 42.9% were DCIS only. The IBTR rate was 4.7% (95% CI, 3.4% to 6.5%) at 5 years, and 10.4% (95% CI, 7.9% to 13.7%) at 10 years.

Table 2 presents univariate and multivariate analyses for the 734 patients with complete data in the MDACC cohort and multivariate

Table 1. Comparison of Patient Demographic, Disease, and Treatment Characteristics in the MDACC and MSKCC Cohorts

Characteristic	Patients in MDACC Cohort		Patients in MSKCC Cohort		
	No. (n = 794)	%	No. (n = 1,868)	%	*P*
Age at diagnosis, years					
Mean	57.7				
Median	57		57		
Range	19-90		25-89		
Ethnicity			NA		
White	607	76.5			
Black	75	9.4			
Other	112	14.1			
Menopausal status					.001*
Pre/perimenopausal	214	27.0	625	33.5	
Postmenopausal	562	70.8	1,187	63.5	
Unknown	18	2.3	56	3.0	
Family history of breast cancer					.8*
No	503	63.4	1,157	61.9	
Yes	291	36.6	688	36.8	
Unknown			23	1.3	
Initial presentation					< .001*
Clinical	160	20.2	251	13.4	
Radiologic	634	79.8	1,588	85.0	
Unknown			29	1.6	
Method of detection			NA		
Microcalcifications	588	74.1			
Density or mass	109	13.7			
Both	62	7.8			
Incidental finding	33	4.2			
Unknown	2	0.3			
Type of image for detection			NA		
Mammography	758	95.5			
Ultrasound/MRI	24	3.0			
No image detection	11	1.4			
Unknown	1	0.1			
Bloody nipple discharge			NA		
Yes	37	4.7			
No	757	95.3			
Tamoxifen use before surgery			NA		
Yes	18	2.3			
No	776	97.7			
Hormone replacement therapy before surgery			NA		
Yes	245	30.9			
No	254	32.0			
Unknown	295	37.1			
Microcalcifications with DCIS			NA		
Pathologic finding only	57	7.2			
Imaging finding only	138	17.4			
Both	514	64.7			
None	85	10.7			
Necrosis with DCIS					.028
Present	471	59.3	1,173	62.8	
Absent	323	40.7	663	35.5	
Unknown			32	1.7	
Nuclear grade					< .001
I	104	13.1	370	19.8	
II/III	631	79.5	1,411	75.5	
Unknown	59	7.4	87	4.7	

(continued in next column)

Table 1. Comparison of Patient Demographic, Disease, and Treatment Characteristics in the MDACC and MSKCC Cohorts (Continued)

Characteristic	Patients in MDACC Cohort		Patients in MSKCC Cohort		
	No. (n = 794)	%	No. (n = 1,868)	%	*P*
Final tumor size, cm			NA		
Mean	1.2				
Median	0.8				
Range	0.09-10				
Final margin					< .001
Negative	698	87.9	1,501	80.3	
Positive/close	93	12.1	360	19.3	
Unknown	3	0.4	7	0.4	
Estrogen receptor			NA		
Positive	289	36.4			
Negative	62	7.8			
Unknown	443	55.8			
Progesterone receptor			NA		
Positive	230	29.0			
Negative	112	14.1			
Unknown	452	56.9			
No. of excisions					
1	591	80.5			
> 1	143	19.5			
Time period of surgery					
1990-1999	262	33.0			
2000-2007	532	67.0			
Adjuvant endocrine therapy					< .001
Yes	256	32.2	398	21.3	
No	538	67.8	1,444	77.3	
Unknown			26	1.4	
Adjuvant radiation therapy					< .001
Yes	576	72.5	906	48.5	
No	218	27.5	935	50.1	
Unknown			27	1.4	
Follow-up time, years					
Mean	7.9				
Median	7.1		5.6		
Range	1-20.4		0-17.5		
IBTR					.028
Yes	63	7.9	202	10.8	
No	731	92.1	1,666	89.2	
IBTR type					
DCIS	36	4.5	122	7	
Invasive with or without DCIS	27	3.4	80	4	
Contralateral breast cancer			NA		
Yes	112	14.1			
No	682	85.9			
MSKCC 5-year probability of recurrence, %					
Mean	6.4				
Median	5				
Range	1-37				
MSKCC 10-year probability of recurrence, %					
Mean	9.9				
Median	7				
Range	2-53				

Abbreviations: DCIS, ductal carcinoma in situ; IBTR, ipsilateral breast tumor recurrence; NA, not applicable; MDACC, MD Anderson Cancer Center; MRI, magnetic resonance imaging; MSKCC, Memorial Sloan-Kettering Cancer Center.
**P* value was calculated after unknown category was excluded.

Table 2. Results of Univariate and Multivariate Cox Proportional Hazards Analysis of Clinicopathologic Variable Influence on IBTR in the MDACC and MSKCC Cohorts

	MDACC Cohort						MSKCC Cohort		
	Univariate Analysis		Multivariate Analysis*				Multivariate Analysis		
Characteristic	HR	*P*	HR	*P*	95% CI		HR	*P*	95% CI
Age at diagnosis	0.99	.3	0.99	.2	0.96	1.01	0.99	.03	0.97 to 0.998
Ethnicity							NA		
White	Referent								
Black	1.16	.7							
Other	0.70	.4							
Family history of breast cancer									
No	Referent								
Yes	1.55	.12	1.62	.09	0.94	2.82	1.34	.07	0.98 to 1.84
Initial presentation									
Radiologic	Referent								
Clinical	1.91	.03	1.87	.039	1.03	3.37	1.39	.09	0.95 to 2.03
Nuclear grade									
I	Referent								
II/III	1.23	.3	1.23	.5	0.67	2.27	1.30	.25	0.84 to 2.02
Necrosis with DCIS									
Absent	Referent								
Present	1.00	.995	1.16	.6	.65	2.05	1.13	.5	0.79 to 1.62
Final margin									
Negative	Referent								
Positive/close	1.06	.9	1.05	.9	.44	2.52	1.73	.002	1.23 to 2.44
Adjuvant endocrine therapy									
Yes	Referent								
No	2.50	.018	2.45	.02	1.15	5.24	2.11	.003	1.29 to 3.46
Adjuvant radiation therapy									
Yes	Referent								
No	1.62	.09	1.59	.1	.88	2.89	2.67	< .001	1.91 to 3.75
Number of excisions									
1	Referent								
> 1	0.72	.5	0.83	.7	.34	2.02	1.68	.03	1.04 to 2.73
Time period of surgery									
1990-1999	Referent								
2000-2007	0.61	.3	0.94	.7	.31	1.28	0.57	< .001	0.41 to 0.79
Grade and radiation									
I/II with radiation	Referent								
I/II without radiation	1.89	.07							
III with radiation	1.38	.4							
III without radiation	1.78	.3							
Final tumor size	1.00	.8							
Adjuvant endocrine therapy if ER positive									
Yes	Referent								
No	6.90	.01							
Adjuvant endocrine therapy if ER negative									
Yes	Referent								
No	2.74	.9							
Adjuvant endocrine therapy if ER unknown									
Yes	Referent								
No	0.93	.9							

NOTE. Total No. = 734.
Abbreviations: C-index, Harrell concordance index; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HR, hazard ratio; IBTR, ipsilateral breast tumor recurrence; NA, not applicable; MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center.
*C-index, 0.68.

analysis from the MSKCC cohort. Omission of endocrine therapy (HR, 2.45; 95% CI, 1.15 to 5.24; $P = 0.02$) and initial presentation on clinical exam (HR, 1.87; 95% CI, 1.03 to 3.37; $P = 0.039$) were significantly associated with increased risk of IBTR. We separated the endocrine therapy results by ER-positive, ER-negative and unknown, and found that omission of endocrine therapy was only significantly associated with increased risk of IBTR in ER-positive DCIS. The univariate association of these two factors with IBTR rate is shown in Figure 1 in

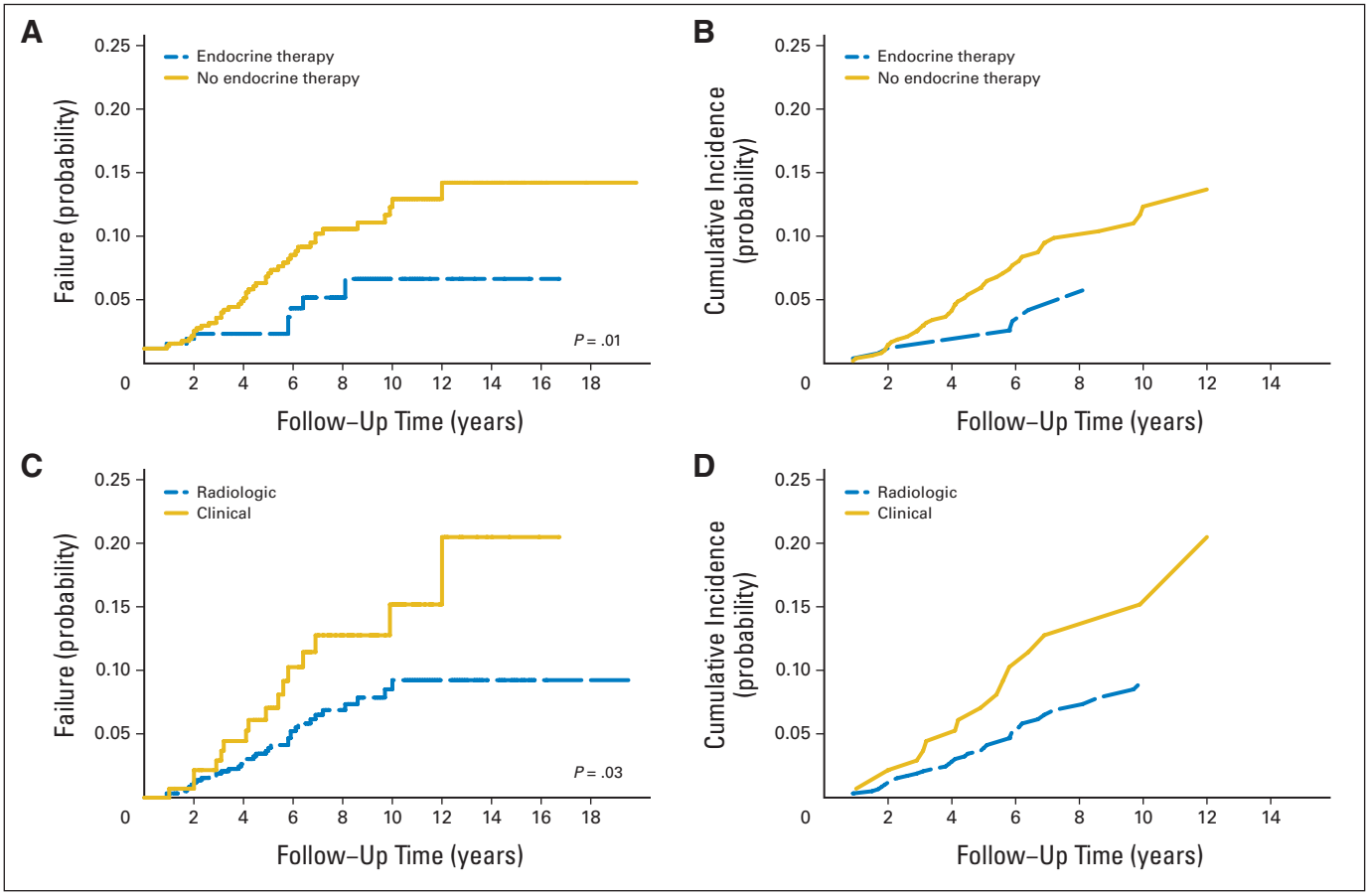

Fig 1. Kaplan-Meier failure and cumulative incidence plots demonstrating association between predictor variables of ipsilateral breast recurrence after breast-conserving treatment for ductal carcinoma in situ. Association of adjuvant endocrine therapy with Kaplan-Meier (A) failure plot and (B) cumulative incidence; and association of initial mode of presentation with Kaplan-Meier (C) failure plot and (D) cumulative incidence. *P* value (log-rank test) is provided for each comparison.

the form of Kaplan-Meier plots and cumulative incidence estimates. The 5-year IBTR rates were 1.2% for patients who received endocrine therapy versus 6.2% without ($P = 0.01$). The 5-year IBTR rates were 7.1% for patients with clinical findings at presentation and 3.9% for patients with radiologic presentation ($P = 0.03$).

No significant association between increased risk of IBTR and presence of necrosis or high nuclear grade was identified. The 5-year IBTR rates were 5.1% for low-nuclear-grade, 3.9% for intermediate-grade, and 5.0% for high-grade tumors. Use of radiation was not significantly associated with a lower IBTR ($P = 0.1$). The 5-year IBTR rates were 3.9% for patients who received radiation therapy and 6.1% for patients who did not.

Evaluating the MSKCC Nomogram

We evaluated our data set with the MSKCC model. Because of missing data, 60 of the 794 patients were excluded. The 5- and 10-year probabilities of recurrence for the 734 patients who had complete data were calculated with the MSKCC nomogram. The median 5-year probability of recurrence was 5% (range, 1% to 37%), and the median 10-year probability of recurrence was 7% (range, 2% to 53%). An ROC curve was drawn to assess the discrimination of the nomogram. The overall predictive accuracy of the nomogram, as measured by the AUC, was 0.634 (95% CI, 0.536 to 0.731) at 5 years, and it was 0.654 (95% CI, 0.572 to 0.734) at 10 years. The Harrell C index was 0.63 (95% CI, 0.55 to 0.72).

To assess the accuracy of the MSKCC nomogram, actual 5- and 10-year recurrences were plotted against the calculated predicted 5- and 10-year probabilities of recurrence for each patient (Fig 2). This shows imperfect calibration, especially in patients with the highest predicted risk, which greatly overestimates the observed risk. Fifty-nine patients (8%) have the highest predicted risk, and 84 patients (11.4%) have the next highest predicted risk, which is estimated rather well by the nomogram. The difference between this group and the next-highest predicted risk is that all 59 patients had no RT, whereas approximately 30% of patients in the next-highest predicted risk group had RT; approximately 70% of patients in this group had surgery before 1999 compared with 37% in the next-highest group; and 32% of patients in this group had positive or close margins compared with 17.8% in the next-highest group.

DISCUSSION

There is a wide spectrum in the practice patterns among physicians for management of DCIS treated with breast conservation.[4] A plethora of clinical and pathologic variables are known to influence the risk of

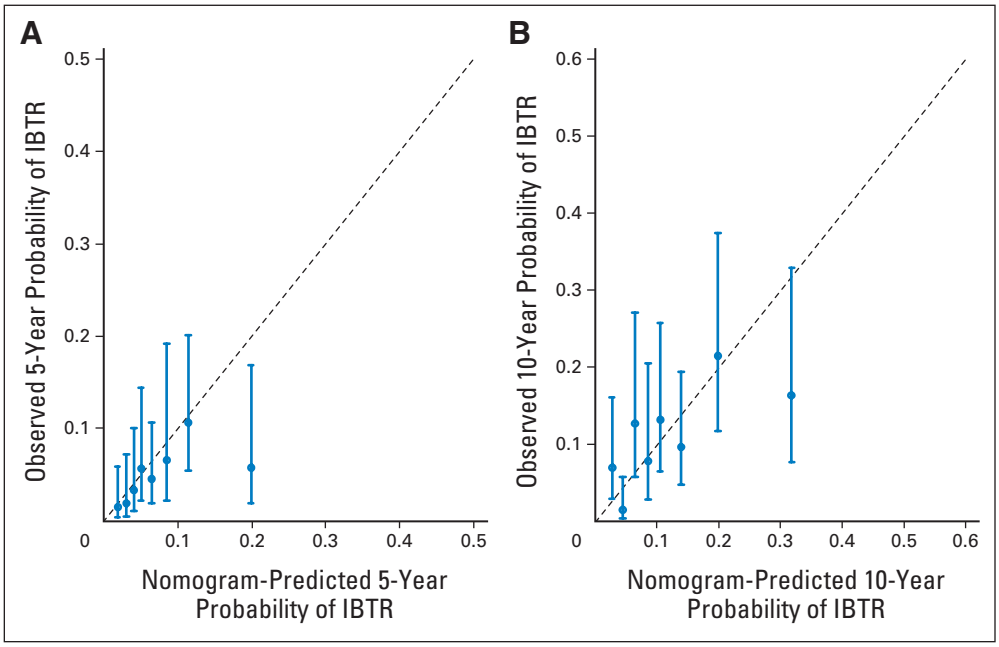

Fig 2. Calibration plots for the nomogram: (A) 5-year nomogram; (B) 10-year nomogram. Patients were grouped by octiles of predicted risk. The *x*-axis is the nomogram-predicted probability of ipsilateral breast recurrence (IBTR). The *y*-axis is the observed probability of IBTR (Kaplan-Meier estimates). Dashed line represents the ideal nomogram; circles represent apparent predictive accuracy, calculated by plotting the mean Kaplan-Meier estimate for each octile versus the mean nomogram-predicted probability for patients in each octile.

IBTR,[6,11] including but not limited to age[5,11,19,20]; clinical presentation[5,11,21]; family history[22]; margin status[3,23]; and histopathologic features, such as extent of DCIS,[24,25] nuclear grade,[5,26] and presence of necrosis and use of RT.[26-28] However, because of variations in study methods, sample sizes, and populations, there is no consensus within the literature on the true risk associated with each of these variables. Consequently, estimating an individual patient's risk of recurrence on the basis of the current literature alone is difficult.

An attractive approach with which to evaluate the risk of IBTR in patients with DCIS after local excision is with the MSKCC nomogram, as described by Rudloff et al.[10] The nomogram is a tool that provides risk estimates as the probability of recurrence at 5 or 10 years. However, the MSKCC nomogram was only internally validated with 200 bootstrap samples, with a concordance probability estimate of 0.668; therefore, applicability to external data sets is unclear.[10] Internal evaluation cannot address the wider issue of the generalizability of the model.[29] Because the goal of validation is to demonstrate satisfactory performance for patients from a population different than the original, it is desirable to evaluate new data collected from an appropriate patient population in a different center. We tested the value of the nomogram with our data set to provide external validation in a completely independent, though similar, setting.

There was no difference with respect to age and family history of breast cancer between the MDACC and MSKCC cohorts. There were marked differences with respect to tumor grade, prevalence of necrosis, initial presentation, final margin status, receipt of endocrine therapy, and use of RT between the two cohorts (Table 1). The biggest difference was that more patients received RT in the MDACC cohort (75% at MDACC *v* 49% at MSKCC; $P < .001$). Follow-up time in the MDACC cohort was longer than in the MSKCC cohort (median, 7.1 years *v* 5.6 years), and the recurrence rate was lower in the MDACC cohort (7.9% *v* 11%).

Our calculated AUC (0.634) and Harrell C index (0.63) showed that the performance of the nomogram is suboptimal. On the basis of the 5-year probabilities of recurrence calibration plot (Fig 2, left), the nomogram seems to overestimate the risk for some patients, because the calculated point is far lower than the reference. We assume that this is mainly because all of those patients in this highest predicted risk group had no RT, and RT is the most important predictor in the MSKCC nomogram but is not a predictor in the MDACC cohort. On the basis of the 10-year probabilities of recurrence calibration plot (Fig 2, right), the accuracy of the nomogram seems to decrease, because more calculated points do not approach the reference line. We assume that this is because follow-up time in the MSKCC cohort is too short (median, 5.6 range 0 to 17.5 years) for calculating 10-year probabilities of recurrence. The primary application of a nomogram is to guide treatment of newly diagnosed patients. However, the prognostic values from the MSKCC nomogram appear to be related to treatment trends over different time periods (eg, use of radiation or endocrine therapy, which can lead to cohort effects). That is, the earlier-diagnosed patients who have more follow-up time are more likely to have observed events when compared with more recently diagnosed patients treated in a different fashion. On the basis of our findings, we conclude that the nomogram leaves significant room for improvement. It is possible that clinical parameters alone are insufficient to predict outcome.

In the study in which the MSKCC nomogram was developed, only six of 10 factors had statistically significant values: age at surgery, use of RT, use of endocrine therapy, margin status, number of excisions, and time period of surgery (Table 2). Our study confirms that endocrine therapy is related to lower recurrence rates after local excision in univariate analysis. Our study supports that patients with ER-positive DCIS will benefit from endocrine therapy. Several large multicenter trials have demonstrated an increased risk of IBTR in patients undergoing local excision without radiation.[3,5,7,8,30] In our study, we found only a trend toward increased risk of IBTR in patients without radiation (hazard ratio, 1.62; $P = .1$), likely as a result of RT in the majority of our patients (75%); the patients who did not undergo RT were more likely to have smaller and lower-grade tumors. We also failed to find evidence showing that positive/close margins increase

IBTR rates; this may be explained by the small number of patients who had positive (0.5%) or close margins (11.2%). The importance of age in the management of DCIS is controversial. Some studies suggest that younger patients with DCIS treated with lumpectomy and RT have a significantly higher risk of local recurrence.[5,11,19,20,31] However, it is uncertain whether this increased risk is related to worse biologic behavior of DCIS in younger patients, to treatment-related factors, or to both possibilities.[31] A number of other studies did not show that young age resulted in a significantly increased risk of local recurrence.[22,32-35] Our study agrees with such findings. Neither our study nor the MSKCC study showed an association between larger tumor size and recurrence of DCIS, whereas other studies have.[24,25] This may be due to selection bias of patients for breast-conserving therapy (tending to be chosen more in patients with small tumors). Similar to the MSKCC study, we did not observe a statistically significant association of any pathologic variables, including grade and presence of necrosis with risk of local failure. Others have also found that there are no significant differences in IBTR rates between those with high grade and necrosis.[10,34,36] However, we found that patients who presented with a palpable mass rather than with radiologic-only presentation had a higher risk of IBTR. Kerlikowske et al[37] also found that detection of DCIS lesions by palpation was one of only two factors most strongly associated with risk of subsequent invasive cancer.

Previously, studies showed that IBTR can be classified into two distinct types of disease: true local recurrences and new ipsilateral primary tumors.[38,39] To accurately assess factors associated with IBTR, it would be of value to separately evaluate those two types. In this study, we were unable to do that because of the small number of patients with IBTR. One of the limitations of our study, like all current studies on predicting IBTR, is the small sample size. Another limitation is that we only used patient, clinical, and pathologic factors to predict probability of IBTR. Molecular factors may help predict probability of IBTR.

In conclusion, DCIS is a heterogeneous disease, and our ability to assess prognosis and predict risk of recurrence on the basis of pathologic and imaging findings is limited. Better decision-making tools are needed to help patients and their providers choose among therapeutic options.[2] A combination of pathologic, clinical, and molecular factors may ultimately reveal more powerful and robust measures for disease classification than any one modality alone.[40]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Min Yi, Funda Meric-Bernstam, Henry M. Kuerer, Elizabeth A. Mittendorf, Anthony Lucci, Kelly K. Hunt
Administrative support: Kelly K. Hunt
Provision of study materials or patients: Isabelle Bedrosian, Kelly K. Hunt
Collection and assembly of data: Min Yi, Sheng Luo, Kelly K. Hunt
Data analysis and interpretation: Min Yi, Isabelle Bedrosian, Rosa F. Hwang, Jaime R. Crow, Kelly K. Hunt
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Baxter NN, Virnig BA, Durham SB, et al: Trends in the treatment of ductal carcinoma in situ of the breast. J Natl Cancer Inst 96:443-448, 2004
2. Allegra CJ, Aberle DR, Ganschow P, et al: National Institutes of Health State-of-the-Science Conference statement: Diagnosis and management of ductal carcinoma in situ September 22-24, 2009. J Natl Cancer Inst 102:161-169, 2010
3. Fisher B, Land S, Mamounas E, et al: Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the National Surgical Adjuvant Breast and Bowel Project experience. Semin Oncol 28:400-418, 2001
4. Ceilley E, Jagsi R, Goldberg S, et al: The management of ductal carcinoma in situ in North America and Europe: Results of a survey. Cancer 101:1958-1967, 2004
5. Bijker N, Meijnen P, Peterse JL, et al: Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: Ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853—A study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 24:3381-3387, 2006
6. Correa C, McGale P, Taylor C, et al: Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010:162-177, 2010
7. Cuzick J, Sestak I, Pinder SE, et al: Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: Long-term results from the UK/ANZ DCIS trial. Lancet Oncol 12:21-29, 2011
8. Emdin SO, Granstrand B, Ringberg A, et al: SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast—Results of a randomised trial in a population offered mammography screening. Acta Oncol 45:536-543, 2006
9. Yen TW, Kuerer HM, Ottesen RA, et al: Impact of randomized clinical trial results in the national comprehensive cancer network on the use of tamoxifen after breast surgery for ductal carcinoma in situ. J Clin Oncol 25:3251-3258, 2007
10. Rudloff U, Jacks LM, Goldberg JI, et al: Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ. J Clin Oncol 28:3762-3769, 2010
11. Fisher B, Dignam J, Wolmark N, et al: Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353:1993-2000, 1999
12. Allred DC, Bryant J, Land S: Estrogen receptor expression as a predictive marker of the effect of tamoxifen in the treatment of DCIS: Findings from NSABP protocol B-24. Presented at 25th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 11-14, 2002
13. Gooley TA, Leisenring W, Crowley J, et al: Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 18:695-706, 1999
14. Hosmer D, Lemeshow S: Applied Logistic Regression (ed 2). New York, NY, Wiley, 2000
15. Gonen M, Heller G: Concordance probability and discriminatory power in proportional hazards regression. Biometrika 92:965-970, 2005
16. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996
17. Harrell FE: Regression Modeling Strategies with Applications to Linear Models, Logistic Regression, and Survival Analysis. New York, NY, Springer-Verlag, 2001
18. Iasonos A, Schrag D, Raj GV, et al: How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 26:1364-1370, 2008
19. Van Zee KJ, Liberman L, Samli B, et al: Long term follow-up of women with ductal carcinoma in situ treated with breast-conserving surgery: The effect of age. Cancer 86:1757-1767, 1999
20. Vicini FA, Kestin LL, Goldstein NS, et al: Impact of young age on outcome in patients with ductal carcinoma-in-situ treated with breast-conserving therapy. J Clin Oncol 18:296-306, 2000
21. Rudloff U, Brogi E, Brockway JP, et al: Concurrent lobular neoplasia increases the risk of ipsilateral breast cancer recurrence in patients with ductal carcinoma in situ treated with breast-conserving therapy. Cancer 115:1203-1214, 2009
22. Hiramatsu H, Bornstein BA, Recht A, et al: Local recurrence after conservative surgery and radiation therapy for ductal carcinoma in situ: Possible importance of family history. Cancer J Sci Am 1:55-61, 1995
23. Silverstein MJ, Lagios MD, Groshen S, et al: The influence of margin width on local control of

ductal carcinoma in situ of the breast. N Engl J Med 340:1455-1461, 1999

24. Silverstein MJ, Lagios MD, Craig PH, et al: A prognostic index for ductal carcinoma in situ of the breast. Cancer 77:2267-2274, 1996

25. Silverstein MJ, Lagios MD: Choosing treatment for patients with ductal carcinoma in situ: Fine tuning the University of Southern California/Van Nuys Prognostic Index. J Natl Cancer Inst Monogr 2010:193-196, 2010

26. Ringberg A, Nordgren H, Thorstensson S, et al: Histopathological risk factors for ipsilateral breast events after breast conserving treatment for ductal carcinoma in situ of the breast: Results from the Swedish randomised trial. Eur J Cancer 43:291-298, 2007

27. Fisher ER, Costantino JP, Leon ME, et al: Pathobiology of small invasive breast cancers without metastases (T1a/b, N0, M0): National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-21. Cancer 110:1929-1936, 2007

28. Fisher ER, Dignam J, Tan-Chiu E, et al: Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 86:429-438, 1999

29. Altman DG, Royston P: What do we mean by validating a prognostic model? Stat Med 19:453-473, 2000

30. Hughes LL, Wang M, Page DL, et al: Local excision alone without irradiation for ductal carcinoma in situ of the breast: A trial of the Eastern Cooperative Oncology Group. J Clin Oncol 27:5319-5324, 2009

31. Vicini FA, Recht A: Age at diagnosis and outcome for women with ductal carcinoma-in-situ of the breast: A critical review of the literature. J Clin Oncol 20:2736-2744, 2002

32. Fowble B, Hanlon AL, Fein DA, et al: Results of conservative surgery and radiation for mammographically detected ductal carcinoma in situ (DCIS). Int J Radiat Oncol Biol Phys 38:949-957, 1997

33. Harris EE, Schultz DJ, Peters CA, et al: Relationship of family history and outcome after breast conservation therapy in women with ductal carcinoma in situ of the breast. Int J Radiat Oncol Biol Phys 48:933-941, 2000

34. Solin LJ, Kurtz J, Fourquet A, et al: Fifteen-year results of breast-conserving surgery and definitive breast irradiation for the treatment of ductal carcinoma in situ of the breast. J Clin Oncol 14:754-763, 1996

35. Szelei-Stevens KA, Kuske RR, Yantsos VA, et al: The influence of young age and positive family history of breast cancer on the prognosis of ductal carcinoma in situ treated by excision with or without radiation therapy or by mastectomy. Int J Radiat Oncol Biol Phys 48:943-949, 2000

36. Silverstein MJ, Cohlan BF, Gierson ED, et al: Duct carcinoma in situ: 227 cases without microinvasion. Eur J Cancer 28:630-634, 1992

37. Kerlikowske K, Molinaro AM, Gauthier ML, et al: Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. J Natl Cancer Inst 102:627-637, 2010

38. Yi M, Buchholz TA, Meric-Bernstam F, et al: Classification of ipsilateral breast tumor recurrences after breast conservation therapy can predict patient prognosis and facilitate treatment planning. Ann Surg 253:572-579, 2011

39. Adepoju LJ, Symmans WF, Babiera GV, et al: Impact of concurrent proliferative high-risk lesions on the risk of ipsilateral breast carcinoma recurrence and contralateral breast carcinoma development in patients with ductal carcinoma in situ treated with breast-conserving therapy. Cancer 106:42-50, 2006

40. Rosai J: Why microscopy will remain a cornerstone of surgical pathology. Lab Invest 87:403-408, 2007

