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ORIGINAL ARTICLE – BREAST ONCOLOGY

Risk Prediction for Local Breast Cancer Recurrence Among Women with DCIS Treated in a Community Practice: A Nested, Case–Control Study

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ABSTRACT

Background. Various patient, treatment, and pathologic factors have been associated with an increased risk of local recurrence (LR) following breast-conserving therapy (BCT) for ductal carcinoma in situ (DCIS). However, the strength and importance of individual factors has varied; whether combining factors improves prediction, particularly in community practice, is uncertain. In a large, population-based cohort of women with DCIS treated with BCT in three community-based practices, we assessed the validity of the Memorial Sloan-Kettering Cancer Center (MSKCC) DCIS nomogram, which combines clinical, pathologic, and treatment features to predict LR.

Methods. We reviewed slides of patients with unilateral DCIS treated with BCT. Regression methods were used to estimate risks of LR. The MSKCC DCIS nomogram was applied to the study population to compare the nomogram-predicted and observed LR at 5 and 10 years.

Results. The 495 patients in our study were grouped into quartiles and octiles to compare observed and nomogram-predicted LR. The 5-year absolute risk of recurrence for lowest and highest quartiles was 4.8 and 33.1 % (95 % CI 3.1–6.4 and 24.2–40.9, respectively; $p < 0.0001$). The overall correlation between 10-year nomogram-predicted recurrences and observed recurrences was 0.95. Compared with observed 10-year LR rates, the risk estimates provided by the nomogram showed good correlation, and reasonable discrimination with a c-statistic of 0.68.

Conclusions. The MSKCC DCIS nomogram provided good prediction of the 5- and 10-year LR when applied to a population of patients with DCIS treated with BCT in a community-based practice. This nomogram, therefore, is a useful treatment decision aid for patients with DCIS.

Various patient, treatment, and pathologic factors have been associated with an increased risk of local recurrence (LR) following breast-conserving therapy (BCT) for ductal carcinoma in situ (DCIS). However, the strength and importance of these individual factors have varied in prior studies and the extent to which combining factors may improve prediction of risk is as yet undetermined.[1–12] Thus, the management of women with DCIS can vary from wide excision alone, wide excision with radiation therapy, to mastectomy; each of these surgical options may be supplemented with adjuvant antiestrogen therapy in women with estrogen receptor (ER)-positive DCIS. Patients and clinicians are understandably bewildered by the therapeutic options available. How best to stratify patients into the appropriate therapeutic algorithms to avoid overtreatment in those women at very low risk for LR and provide sufficient treatment in women at high risk for recurrence remains an ongoing challenge.

In 2010, Rudloff and colleagues from Memorial Sloan-Kettering Cancer Center (MSKCC) published a nomogram for predicting the risk of LR after breast-conserving surgery for DCIS.[13] The nomogram was developed using the data from 1681 patients with DCIS treated with breast-

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conserving surgery at MSKCC. Using Cox regression analyses, the authors identified ten clinical, pathological and treatment variables, including age, family history, presentation (clinical vs. radiological), treatment with radiation therapy and/or hormonal therapy, DCIS nuclear grade, presence or absence of necrosis, margin status, number of excisions and year of surgery—useful in developing a model that could predict the probability of ipsilateral breast tumor recurrence at 5 and 10 years.[13] The model was internally validated using bootstrapping with 200 samples resulting in good validation with a concordance index (C-index) of 0.704 (bootstrap validated to 0.688) and a concordance probability estimate (CPE) of 0.686 (bootstrap validated to 0.671).[13] Whereas others have investigated the utility of the nomogram among patients treated in academic centers, we sought to test the reliability of the MSKCC nomogram model for the first time using a community-based population of DCIS patients treated with BCT with known outcome.[14–16] We also review the literature on this nomogram and synthesize the prior validations.

MATERIALS AND METHODS

The study was conducted in three study sites that participate in the Cancer Research Network (CRN), a National Cancer Institute-funded consortium of 14 health care delivery sites with a goal to foster collaborative research in cancer among diverse populations and health care systems. Approval for this study was given by each of the participating institutions.

The study population and methods have been described in detail in prior publications from this group (see references).[17,18] In brief, we identified all patients diagnosed with a first primary unilateral DCIS between 1990 and 2001 treated with BCT at Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), and Harvard Pilgrim Health Care (HPHC).[17,18] Patients <85 years at diagnosis with no prior invasive cancer (breast or other site) were eligible for inclusion in the parent study.[17,18] Patients who received a mastectomy <6 months after their index DCIS and those with breast cancer in the contralateral breast at the time of diagnosis with the index DCIS were excluded.[17,18] LRs were defined as DCIS or invasive cancer in the ipsilateral breast at least 6 months after the index diagnosis.[17,18] For efficiency of resources, a case–control study was conducted within the full cohort of 2995 patients from the parent study. This study design is commonly used to examine risk factors in relation to disease outcomes in well-defined cohorts when covariates of interest cannot be measured on the entire population due to time/cost constraints. In general all cases (i.e., recurrences) are sampled, with random sampling of non-cases (controls). Cases with recurrences were identified within the full cohort of women who had DCIS in 1990–2001, and for each case, up to two matched controls were selected from among those in the cohort who had not had a recurrence by the time of the case's recurrence. Controls were individually matched to their case on health plan, age at diagnosis, and calendar year of diagnosis. Pathology review of patient histologic material was performed for all cases and matched controls by LC and SS. Complete data for application of the MSKCC nomogram was available for 190 pathology confirmed DCIS patients with recurrences (cases) and 305 women with DCIS without recurrences (controls). The MSKCC DCIS nomogram was applied to each subject to compare the nomogram-predicted and observed risks for LR at 5 and 10 years using the website designed by MSKCC[13] (http://nomograms.mskcc.org/Breast/DuctalCarcinomaInSituRecurrencePage.aspx) The metrics used in the web-based nomogram, developed from the original published nomogram, include age at diagnosis, family history (yes, if first or second degree relative with breast cancer), presentation (radiologic or clinical), adjuvant radiation therapy (yes/no), adjuvant endocrine therapy (yes/no), nuclear grade (low vs. intermediate or high), necrosis (yes, if present), margins (negative if at least 2 mm vs. close/positive), number of surgical excisions (1–4), and year of surgery (1991–present).

Statistical Methods

Univariate analysis was used to evaluate clinical and pathologic features associated with risk of LR. The MSKCC nomogram-predicted, 5- and 10-year probabilities of recurrence were obtained for each patient using the website prediction tool. These nomogram probabilities were then grouped in two different ways: as quartiles and octiles. Methods developed by Langholz and Borgan for nested case-control data were used to estimate the LR for each quartile and octile at 5 and 10 years and the corresponding 95 % confidence intervals.[19] Conceptually, this approach utilizes sample selection probabilities associated with the case-control sampling scheme from the well-defined parent cohort for weighting in a generalized Kaplan–Meier estimator of cumulative recurrence probabilities (i.e., absolute risk [AR]). These ARs were then compared to the mean nomogram-predicted probabilities per quartile or octile. The ability of the nomogram score to discriminate between cases and controls was measured by a concordance statistic which extends the usual concordance statistic (c-statistic) applied in unmatched case-control studies [area under the receiver operating characteristic (ROC) curve (AUC)] to accommodate the matching in the study design.[20] These data were plotted and a curve generated to depict discrimination.

RESULTS

The median age of the 495 subjects in the study population was 57 (range 33–84) years, and the median length of follow-up was 5.3 (range 0.5–15.4) years. The characteristics of the study population are summarized in Table 1. The only pathologic features associated with increased LR in univariate analysis were larger lesion size (relative risk [RR] = 3.6 for ≥20 low-power fields of DCIS; 95 % CI 1.6–7.8) and involved (RR = 2.9; 95 % CI 1.5–5.6) or close (<1 mm; RR = 2.9; 95 % CI 1.8–4.6) margins.[18] The overall 5- and 10-year LR rates for the whole cohort

TABLE 1 Clinical and pathologic characteristics of study population

Patient/clinical features	Cases ($N = 190$)		Controls ($N = 305$)	
	N	%	*N*	%
Follow-up (year)				
Median	3.0		8.0	
Range	0.5–13.3		1.1–15.4	
Age (year)				
Median	56		56	
Range	35–84		33–83	
Initial presentation				
Radiologic	153	80.5	251	82.3
Clinical	37	19.5	54	17.7
Radiation therapy use				
No	131	68.9	135	44.3
Yes	59	31.1	170	55.7
Tamoxifen use				
No	186	97.9	281	92.1
Yes	4	2.1	24	7.9
Histopathologic features necrosis				
None	44	23.2	84	27.5
Punctate	27	14.2	34	11.1
Comedo	119	62.6	187	61.3
Predominant nuclear grade				
Low	17	8.9	30	9.8
Intermediate	106	55.8	161	52.8
High	67	35.3	114	37.4
Size (no. of low-power fields with DCIS)				
1	15	7.9	50	16.4
2–5	44	23.2	83	27.2
6–9	28	14.7	47	15.4
10–14	34	17.9	40	13.1
15–19	23	12.1	22	7.2
20+	46	24.2	63	20.7
No. of excisions				
1	88	46.3	114	37.4
2	91	47.9	179	58.7
3+	11	5.8	12	3.9
Margins by review				
Negative ≥3 mm, negative reexcision	56	29.5	156	51.1
Negative, 1–2.9 mm	22	11.6	25	8.2
Negative, unknown mm	7	3.7	13	4.3
Close, <1 mm	76	40.0	82	26.9
Positive (ink on DCIS)	29	15.3	29	9.5

TABLE 2 5- and 10-year risk of local recurrence among DCIS women in relation to MSKCC DCIS nomogram-predicted probability (in quartiles and octiles)

Nomogram-predicted probability of LR	5-year risk				10-year risk			
	Women with recurrences: cases	Women without recurrences: controls	% observed LR	95 % CI	Women with recurrences: cases	Women without recurrences: controls	% observed % LR	95 % CI
Quartile 1	17	85	4.8	3.1–6.4	24	95	8.2	5.6–10.8
Quartile 2	34	88	8.5	6.1–10.7	33	93	12.1	8.8–15.2
Quartile 3	61	75	20.9	15.4–26.1	62	64	34.2	26.1–41.4
Quartile 4	78	57	33.1	24.2–40.9	71	53	44.0	33.6–52.8
Octile 1	7	33	4.3	1.8–6.8	9	49	5.8	2.9–8.7
Octile 2	10	52	4.9	2.7–7.0	15	46	10.9	6.3–15.2
Octile 3	19	47	7.7	4.7–10.6	13	37	9.8	5.4–14.1
Octile 4	15	41	9.3	5.6–12.8	20	56	13.9	9.2–18.4
Octile 5	35	47	18.7	12.8–24.1	25	29	31.6	20.8–41.0
Octile 6	26	28	25.2	15.8–33.5	37	35	39.4	27.2–49.6
Octile 7	32	32	24.9	16.1–32.8	27	30	31.1	20.6–40.2
Octile 8	46	25	43.5	28.9–55.1	44	23	61.5	43.0–74.0

Quartile groups 1–4 for 5-year probability of recurrence are: 2–7, 8–12, 13–19, 20–53 %, respectively

Quartile groups 1–4 for 10-year probability of recurrence are: 3–12, 13–20, 21–30, 31–70 %, respectively

Octile groups 1–8 for 5-year probability of recurrence are: 2–5, 6–7, 8–10, 11–12, 13–16, 17–19, 20–26, 27–53 %, respectively

Octile groups 1–8 for 10-year probability of recurrence are: 3–9, 10–12, 13–16, 17–20, 21–24, 25–30, 31–39, 40–70 %, respectively

were 7.8 and 12.9 %, respectively. These results have been reported in detail in a prior publication from this cohort.[18]

When applied to our study population, the overall correlation between 5- and 10-year nomogram-predicted recurrences and observed recurrences was 0.98 and 0.95, respectively. This represents high correlation with the observed rates of LR.

In order to compare the observed with the nomogram-predicted probabilities, the study population was grouped into both quartiles and octiles (Table 2). The 5-year AR of recurrence was 4.8 % for quartile 1 (95 % CI 3.1–6.4), 8.5 % for quartile 2 (95 % CI 6.1–10.7), 20.9 % for quartile 3 (95 % CI 15.4–26.1), and 33.1 % for quartile 4 (95 % CI 24.2–40.9; $p < 0.0001$). The 10-year AR of recurrence was 8.2 % for quartile 1 (95 % CI 5.6–10.8), 12.1 % for quartile 2 (95 % CI 8.8–15.2), 34.2 % for quartile 3 (95 % CI 26.1–41.4), and 44.0 % for quartile 4 (95 % CI 33.6–52.8). The observed and nomogram-predicted 5- and 10-year risks are plotted against one another in Fig. 1. The calibrations between the nomogram-predicted and the observed LR rates were maintained when the analyses were restricted to patients treated with and without radiation therapy (data not shown).

A subset of the study population had sufficient follow-up (≥10 years) to allow comparison of the percentage distribution of the 10-year nomogram-predicted risk of recurrence for women who had a recurrence (Fig. 2; cases in red: $n = 187$) and those who did not have a recurrence (controls in green: $n = 68$) at 10 years. As shown from the curves, there is some overlap of women with and without recurrences, but the figure does show that nearly 60 % of those without a recurrence at 10 years had 10-year predicted risks of less than 20 % and that >70 % of those with a recurrence at 10 years had a 10-year predicted risk of ≥20 %. The concordance (c-statistic) is relatively high at 0.68, indicating that the nomogram has moderate predictive value.

DISCUSSION

In this validation study, we found that the MSKCC DCIS nomogram performs well on a population of women with DCIS treated with BCT in community-based practices, providing excellent correlation and calibration and moderately good discrimination. This tool combined several known risk factors for LR, following a diagnosis of DCIS. The information needed is commonly acquired clinical, pathological, and treatment factors; as such, the nomogram can be used to facilitate an individualized treatment plan for women with DCIS. Clinicians can determine predicted risks of LR both with and without radiation therapy and with and without endocrine therapy by varying these treatment parameters in the web-based prediction tool, thereby allowing a more informed discussion with the patient regarding risk-benefit ratios of each treatment option.

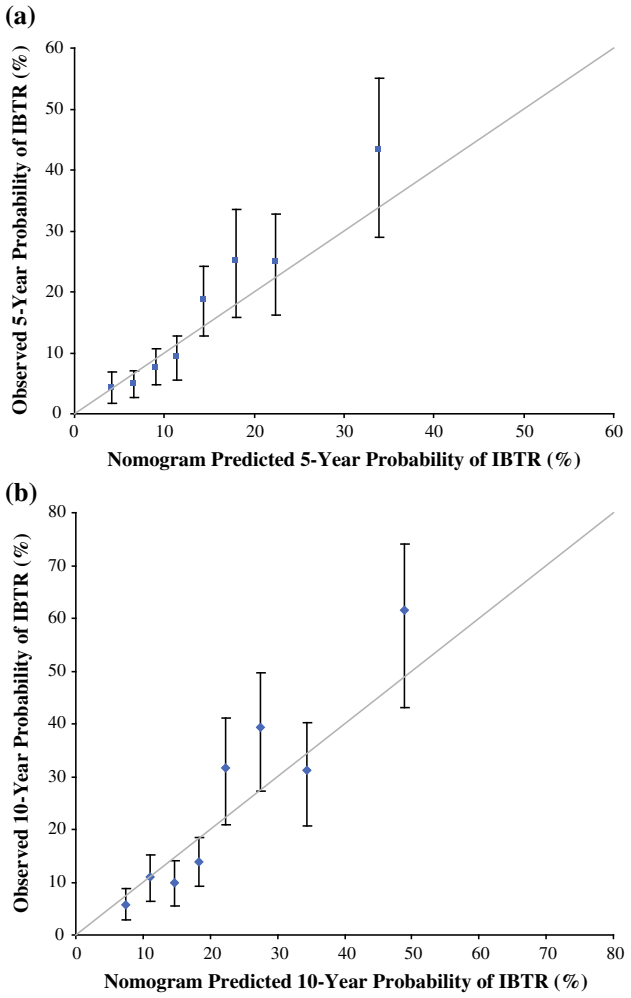

FIG. 1 Observed versus nomogram-predicted 5-year (**a**) 10-year (**b**) probability of an ipsilateral breast tumor recurrence (IBTR) (in octiles). *Gray line* is when observed = predicted

We found the 5-year AR of recurrence for the lowest and highest quartiles of nomogram-predicted recurrence were 4.8 and 33.1 % (95 % CI 3.1–6.4 and 24.2–40.9, $p < 0.0001$), respectively. The overall correlation of 10-year nomogram-predicted and observed recurrences was 0.95. Compared with the observed 10-year LR rates, the risk estimates provided by the nomogram showed good correlation, reasonable discrimination, and a c-statistic of 0.68. Knowing that 33 % of a group of women are likely to develop a LR compared with only 4.8 % is of tremendous value, and most clinicians would counsel and manage those two groups of patients differently.

Two other studies have evaluated the MSKCC DCIS nomogram among populations of patients from large academic centers.[14,15] Yi and colleagues tested the nomogram on 734 women with DCIS treated with BCT at the MD Anderson Cancer Center. The median 5-year probability of recurrence was 5 % (range 1–37 %), and the 10-year

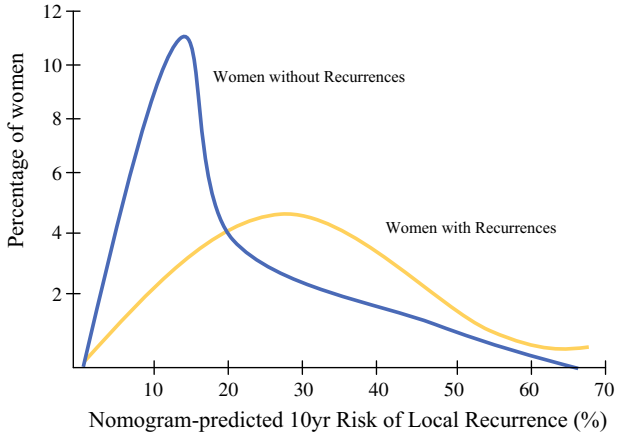

FIG. 2 Percentage distribution of MSKCC DCIS nomogram-predicted 10-year risk for women with (*yellow*) and without (*blue*) recurrences

probability of recurrence was 7 % (range 2–53 %), with a predicted discrimination of the nomogram of 0.634 (95 % CI 0.536–0.731) at 5 years and 0.654 (95 % CI 0.572–0.734) at 10 years as measured by the area under the curve (AUC) on receiver-operator curves (ROC).[14] Sweldens et al. studied 467 women with DCIS treated with BCT; the nomogram gave a concordance index (C-index) and a concordance probability estimate (CPE) of 0.66 and 0.61, respectively.[15] These AUC and concordance values are comparable to those reported for the Oncotype*DX*® Recurrence Score (0.69), the Gail model (0.58), and Adjuvant! Online (www.adjuvantonline.org) (0.56) for invasive cancers.[21–23]

A third study used the MSKCC DCIS nomogram to develop a nomogram in an Asian population of women with DCIS, demonstrating a C-index of 0.67 for the MSKCC nomogram and 0.70 for their National Cancer Center Singapore (NCCS) nomogram (with internal validation and bootstrapping, incorporating age at surgery, adjuvant endocrine therapy, and presence of necrosis found to be significantly associated with ipsilateral breast tumor recurrence).[16] The authors used decision curve analyses to evaluate the performance of both nomograms, demonstrating that each performed well, although at slightly differing thresholds.[16,24]

Van Zee and colleagues have argued that calibration (i.e., how closely the predicted risk is to the observed risk) rather than the AUC is most important in patient management decisions using models, such as the DCIS nomogram.[23] Calibration measures the degree to which a model accurately predicts the *proportion* of a group of patients that will develop the outcome.[25] As such, the calibration could be (and often is) quite high (near 1.00) without being of clinical value for individual patient management (although we found it useful in our study).

TABLE 3 Comparison of features of studies applying MSKCC DCIS nomogram

Characteristic Study period	MSKCC[13] 1991–2006	MDACC[14] 1990–2007	UH Leuven[15] 1973–2010	NCC Singapore[16] 1992–2011	Current study controls[a] 1990–2001
Median age (year)	57	57	56	49	56
Median F/U (year)	5.6	7.1	7.2	5.9	8.0
Postmenopausal (%)	63.5	70.8	65	33.1	63.9
Radiologic presentation (%)	85.0	79.8	82	54.3	82.3
Nuclear grade 1 (%)	19.8	13.1	19	27.4	9.8
Nuclear grade 2 or 3 (%)	75.5	79.5	76	72.0	90.2
Necrosis present (%)	62.8	59.3	48	49.2	72.4
Final margin negative (%)	80.3	87.9	50	71.5	90.5
% receiving radiation therapy	48.5	72.5	99	95.1	55.7
% receiving endocrine therapy	21.3	32.2	37	51.8	7.9

[a] In a nested-case control study, controls are selected randomly to represent the population from which the cases arise

Concordance (which is closely related to AUC) *discriminates* among women who will and will not develop recurrence. Figure 2 shows the MSKCC nomogram discriminates rather well, although not perfectly, in separating women with DCIS who developed recurrences from those that did not in our study. In contrast, data plotted in a similar manner for other prediction models, such as the Gail model, often show considerable overlap of the two curves indicating that the model is not able to reliably discriminate those who will develop recurrences from those who will not.[22,25]

There are a number of similarities between the Yi and Sweldens studies and the current study (Table 3), with a similar median age and length of follow-up, proportion of postmenopausal women, racial distribution (where reported), and proportion of patients presenting radiographically (between 80 and 85 %).[19,20] The MSKCC and UH Leuven study have similar proportions of patients with DCIS nuclear grade 1, whereas the current study had a lower proportion of patients with low nuclear grade DCIS. Differences include treatment strategies; patients treated at MD Anderson were considerably less likely to have had more than one excision (19.5 vs. 62.6 % for the current study). Only 50 % of women in UH Leuven had negative final margins compared with 63.6–87.9 % at the other sites, but nearly all patients received radiation therapy (99 vs. 48.5–72.5 % at the other sites).

Identification of newer molecular methods that are able to stratify patients with DCIS by risk for recurrence better than standard pathological factors is an area of ongoing research. One such test is the Oncotype*DX*® DCIS Score (from Genomic Health, Inc.). This test utilizes 12 genes from the original Oncotype*DX*® recurrence score assay for invasive breast carcinoma to provide low-, intermediate-, and high-risk groups with 10-year predicted risks of recurrence of in situ or invasive carcinoma of 12, 24.5, and 27.3 %, respectively.[26] In a recent report from an independent population, the test performed similarly, although no calibration curves are provided in either study to compare Oncotype*DX*® to other predictive models.[26,27] Others have proposed a panel of immunohistochemical markers—p16, COX-2, and Ki-67—to predict which patients are likely to progress to invasive carcinoma, although the magnitude of risk conferred by these various combinations of markers is still low and is comparable to that of standard pathologic factors.[28] A highly discriminating biomarker remains elusive.

CONCLUSIONS

Our study demonstrates that the MSKCC DCIS nomogram provides reliable prediction of LR for women with DCIS being treated with breast-conserving surgery and more specifically discriminates moderately well those patients who are likely to recur from those who are not. Furthermore, ours is the first study to validate use of this tool among women treated in community-based practices with known outcome. Given the modest relative risks associated with other known clinical and pathological factors, this model offers a readily applicable tool for the patient-clinician conversation regarding management of DCIS both with and without radiation therapy.

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