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Validation of the Kattan Nomogram for Prostate Cancer Recurrence After Radical Prostatectomy

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Abstract

Background—The Kattan postoperative radical prostatectomy (RP) nomogram is used to predict biochemical recurrence-free progression (BCRFP) after RP. However, external validation among contemporary patients using modern outcome definitions is limited.

Methods—A total of 1,931 patients who underwent RP at Roswell Park Cancer Institute (RPCI) between 1993 and 2014 (median follow-up, 47 months; range, 0–244 months) were assessed for NCCN-defined biochemical failure (BF) and RPCI-defined treatment failure (TF). Actual rates of biochemical failure-free survival (BFS; defined as 1 – BF) and treatment failure-free survival (TFS; defined as 1 – TF) were compared with Kattan BCRFP nomogram predictions.

Results—The Kattan BCRFP nomogram predictions at 5 and 10 years were predictive of BFS (area under the receiver operating characteristic curve [AUC], 0.772) and TFS (AUC, 0.774). The Kattan BCRFP nomogram tended to underestimate BFS and TFS compared with actual outcomes. The Kattan 5-year BCRFP predictions consistently overestimated actual 5-year BFS outcomes among subgroups of high- and intermediate-risk patients with at least 5-year outcomes.

Conclusions—The Kattan BCRFP nomogram is a robust predictor of NCCN-defined BF in a large sample of patients with RP with substantial follow-up and modern, standardized failure definitions

Background

Prostate cancer remains one of the most frequently diagnosed forms of cancer in the United States, with a 5-year survival rate approaching 100%.¹ Distinguishing the aggressive from

the clinically indolent forms of the disease at diagnosis remains difficult.^{2–5} Genetic and molecular markers for aggressive prostate cancer have improved,^{6,7} but clinical nomograms continue to provide the most accurate tools to identify patients most likely to experience poor outcomes.^{8–10}

The prostate cancer risk nomograms developed by Kattan et al¹¹ use clinical and pathologic variables to predict probability of biochemical recurrence-free progression (BCRFP) after radical prostatectomy (RP). The Kattan BCRFP nomogram (previously referred to as the *Kattan postoperative nomogram*) has been validated in multiple studies.^{9,11–16} Some of these studies used patient data for both training and validation,^{9,11,12} and some used patient data entirely for external validation.^{13–16} Regardless of the study goal, all studies used older and often institution-defined RP failure definitions. In one multi-institutional study, a single failure definition was used even though each institution used different criteria.¹⁴ In addition, number of patients, follow-up duration, and treatment era vary greatly. In this study, clinical and pathologic characteristics were collected from 1,931 patients treated with RP at Roswell Park Cancer Institute (RPCI) between 1993 and 2014 in order to perform an entirely external validation of the Kattan nomogram and where modern, standardized failure definitions were used. Actual outcomes were compared with outcomes predicted by the Kattan BCRFP nomogram.

Methods

Patient and Data Collection

After approval from the RPCI Institutional Review Board, a prospectively maintained database of 1,931 patients who had undergone open or robotic RP at RPCI between January 5, 1993, and February 27, 2014, was queried. Two different oncologic measures were used to assess failure: (1) NCCN-defined biochemical failure (BF; “failure of prostate-specific antigen [PSA] to fall to undetectable levels,”¹⁷ defined as PSA persistence; or “undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations,”¹⁷ defined as PSA recurrence); and (2) RPCI-defined treatment failure (TF; either BF or additional treatment after RP without meeting the BF definition). TF should be considered because some patients begin treatment when BF appears imminent but criteria have not yet been met. Among the patients studied herein, multiple patients were treated as having BF, even though they did not meet BF criteria. Most of these patients were treated during the period after PSA sensitivity was increased (at RPCI, this change occurred in late 1997) but before failure definitions were revised to reflect the increased PSA sensitivity (at RPCI, this was physician-dependent, but by 2005, most RPCI physicians had adopted the NCCN definition of BF). Although this situation was rare among patients in this database (approximately 80 patients [4%] fell into this category), it is important to consider these patients, because not including them could underestimate the true rate of BF. Annotating data included clinical stage and Gleason score; RP date; pathologic stage and Gleason score; margin and lymph node status; pre- and post-RP serum PSA levels and prostate cancer–related treatments and dates before or after RP. Changes in the AJCC Cancer Staging Manual in 1997¹⁸ and 2002¹⁹ created ambiguity within clinical stage T2, which was resolved by staging all patients who underwent RP before 2002 using the 2002 AJCC

Staging Manual.¹⁹ All patients were followed by patient, urologist, and/or primary care practitioner correspondence, to track outcome. Biochemical failure-free survival (BFS) and treatment failure-free survival (TFS) were determined by subtracting BF or TF percentages from one (ie, BFS = 1 – BF; TFS = 1 – TF) and compared with Kattan BCRFP nomogram predictions.

Statistical Analysis

Outcome probabilities predicted by the Kattan BCRFP nomogram were compared with actual patient outcomes by dividing patients into quintiles and taking the average predicted outcome probability and comparing with the actual outcome average, which used the method developed by Harrell et al.²⁰ The area under the receiver operating characteristic curve (AUC) was calculated as an additional measure of accuracy.²⁰ Subgroup analysis was performed on patients with high-risk or intermediate-risk prostate cancer using 3 parameters, as defined by NCCN.¹⁷ NCCN risk groupings use clinical Gleason sum and clinical tumor stage; in this study, pathologic Gleason sum and pathologic tumor stage were used instead because they are considered more accurate and were available for all patients. High-risk was defined as diagnostic PSA level greater than 20 ng/mL, pathologic Gleason sum of 8 or greater, or pathologic tumor stage of pT3 or higher. Comparisons were made individually for each of the 3 high-risk parameters, as well as overall high risk (patients had at least 1 of the 3 high-risk parameters). Intermediate-risk was defined as a PSA level greater than 10 but less than or equal to 20 ng/mL, Gleason sum of 7, or pathologic tumor stage of T2b or T2c.¹⁷ As with the high-risk analysis, comparisons were made individually for each of the 3 intermediate-risk parameters, as well as overall intermediate risk (patients had at least 1 of the 3 intermediate-risk parameters, but none of the high-risk parameters). This subgroup analysis was limited to patients with known outcome at 5 years; average predicted BCRFP at 5 years for each group was compared with actual 5-year BFS.

Results

The clinical and pathologic characteristics of the 1,931 study patients are shown in Table 1. The median follow-up time for the entire cohort was 47 months (range, 0–244 months). A total of 811 patients (42%) had at least one high-risk oncologic risk feature (diagnostic PSA level >20 ng/mL; pathological Gleason sum ≥ 8; or pathologic stage ≥ pT3). A total of 436 patients (23%) were classified as having BF, 516 (27%) as having TF, and 74 (4%) as having distant metastatic prostate cancer. A total of 170 patients (9%) died: 24 (1%) from prostate cancer and 146 (8%) from other causes.

Patients were divided into quintiles based on BCRFP at 5 years and at 10 years. The Kattan BCRFP nomogram predictions for 5 and 10 years were compared with actual outcomes for BFS (Figure 1) and TFS (Figure 2). The AUC was 0.772 for BFS and 0.774 for TFS. BCRFP predictions tracked closely, with both BFS and TFS at 5 and 10 years for all quintiles, although the nomogram tended to overestimate actual BCRFP. The 10-year nomogram predictions were within the 95% confidence intervals (CIs) of BFS (Figure 1B).

High-risk subgroups (diagnostic PSA level >20 ng/mL, pathologic Gleason sum ≥ 8, pathologic stage ≥ pT3, or overall high risk, defined as having ≥ 1 high-risk parameter) were

identified so that BCRFP predictions could be compared with actual outcomes at 5 years in the patients at greatest risk for recurrence (Figure 3). Only those patients who had known outcome at 5 years were included in this analysis; 927 (48%) of 1,931 patients could be used and 543 (or 59%) were BFS. Average BCRFP at 5 years was 0.49, whereas actual BCRFP at 5 years was 0.21 for the 52 patients with a diagnostic PSA level greater than 20 ng/mL. For 143 patients with pathologic Gleason sum of 8 or greater, the average BCRFP at 5 years was 0.53; the actual BFS at 5 years was 0.23. BCRFP predictions at 5 years for 372 patients with pathologic stage pT3 or pT4 (mean, 0.66) overestimated the actual BFS at 5 years (mean, 0.28). For the overall high-risk group (417 patients), the 5-year prediction average (mean, 0.67) overestimated the actual 5-year BFS (mean, 0.31). All comparisons showed significantly different means ($P<.001$).

Intermediate-risk subgroups (diagnostic PSA level >10 but ≤ 20 ng/mL, pathologic Gleason sum = 7, pathologic stage = pT2b or pT2c, or overall intermediate-risk, defined as 1 intermediate-risk parameter, but no high-risk parameters) were identified to compare with BCRFP predictions at 5 years for the group of patients that constituted the bulk of modern patients with prostate cancer (Figure 4). As with the high-risk analysis, only data from patients who had known outcomes at 5 years were used (927 [48%] of the original 1,931). For 98 patients with a diagnostic PSA between 10 and 20 ng/mL, BCRFP predictions at 5 years (mean, 0.64) overestimated the actual BFS at 5 years (mean, 0.41). The 5-year predictions (mean, 0.90) for the 454 patients with pathologic Gleason sum 7 (this includes both Gleason grade = “3+4” and “4+3”) overestimated the actual BFS at 5 years (mean, 0.79). For 507 patients with pathologic tumor stage pT2b or pT2c, BCRFP predictions for 5 years (mean, 0.81) overestimated the actual BFS at 5 years (mean, 0.55). For 479 patients having any intermediate-risk parameter (but no high-risk parameters), 5-year BCRFP predictions (mean, 0.91) overestimated the actual BFS at 5 years (mean, 0.81). All comparisons showed different means ($P<.001$).

Discussion

The Kattan BCRFP nomogram has been shown to correlate well with actual RP outcomes in several studies, some of which used patient data for both training and validation,^{9,11,12} and some of which used patient data solely for external validation (Table 2).^{13–16} Among the studies that used patient data for both training and validation, agreement between actual outcomes and predicted outcomes was very good. This is not surprising, because patients from the same institution are often treated by the same physicians and tend to have similar outcomes. The most rigorous validation of a nomogram comes from a large group of patients from an institution that is different from the one used for training. Among the previous external validation studies, large numbers of patients were sometimes used, but without application of a uniform TF definition.^{14,16} In another external validation study, the failure definition was standardized, but patient number was relatively low.¹⁵ In all previous studies, patients treated at the beginning of the PSA era were compared with those treated much later, which can be problematic because of changes in PSA test sensitivity and thresholds for adjuvant and/or salvage treatment. Increases in PSA test sensitivity caused some clinicians to treat patients before their PSA level reached what was considered BF. All studies used an older definition of failure (PSA level >0.2 or 0.4 ng/mL) instead of a more

modern one. Given these changes over time, the standardization of outcome measures becomes more important in assessing the predictive quality of nomograms for current and future patients. This study tested the external validation of the Kattan BCRFP nomogram for 1,931 patients treated at RPCI using the NCCN BF definition and the RPCI TF definition. This study combined substantial follow-up duration (median, 47 months) of a relatively large group of patients who underwent RP (1,931) who were evaluated with standardized, modern definitions of outcome, and clearly defined clinical and pathologic characteristics.

The decision to study RPCI-defined TF in addition to the more widely accepted BF was based on the following rationales: (1) the failure definition used in several of the previous validation studies to compare with the Kattan BCRFP nomogram predictions included patients who had post-RP treatments but did not have biochemical recurrence, and (2) several cases of patients who underwent RP at RPCI received salvage treatment before NCCN-defined BF was reached, and likely would have experienced BF if modern PSA tests and standard BF definitions had been used. As an example, a patient who underwent RP in mid-2002 had an undetectable PSA level (<0.03 ng/mL) at the 3-month follow-up, then a PSA level of 0.21 ng/mL at the 6-month follow-up. At the 9-month follow-up visit, the PSA level was 0.48 ng/mL. No other PSA levels were recorded, but at 10 months, he received radiation therapy, and his PSA level returned to undetectable levels (<0.03 ng/mL). This patient would not be considered as having BF based on the NCCN definition, but given this PSA and treatment history, primary treatment certainly failed. There are 80 patients (4% of the 1,931) who did not experience BF based on the stricter NCCN definition, but fell into a gray area in which longer follow-up, or more PSA testing, before salvage radiation or androgen deprivation therapy would have confirmed BF using the NCCN definition. Analyzing them as a separate group to compare with BCRFP predictions appeared worthwhile. All patients who were categorized as BF are also TF; however, TF includes a small group of patients (80) who were not categorized as BF.

The Kattan BCRFP nomogram performed well compared with actual outcomes. Predictions of BCRFP for both 5 and 10 years tracked closely with BFS, and the 10-year average BCRFP predictions were all within 95% CI of BFS. BCRFP predictions were not as accurate in predicting TFS; most of the 5- and 10-year predictions do not fall within the 95% CI of TFS. When the nomogram did not match actual outcomes, it overestimated the treatment success rate. Several other studies also have reported that the Kattan BCRFP nomogram tends to overestimate the disease-free survival rate.^{9,12,13,15}

An increasing trend for active surveillance of patients with low-risk prostate cancer follows the recommendation from the American Urological Association (AUA),²¹ NCCN,²² and the European Association of Urology (EAU).²³ RP cohorts from contemporary urology practices may include a higher proportion of high-risk patients relative to the historical cohorts used to develop and validate the Kattan nomogram. Whether the Kattan BCRFP nomogram has predictive accuracy in a contemporary RP cohort with more common high-risk features remains unknown. For this reason, a subanalysis was performed in the current study that compared the predicted 5-year BCRFP for high-risk patients (diagnostic PSA >20 ng/mL, pathologic Gleason sum ≥ 8 , pathologic tumor stage = pT3 or pT4, or overall high risk, defined as any high-risk parameter) versus the actual 5-year BFS for patients whose 5-

year outcome was known. The relatively high recurrence rate among this subgroup (41% BF, or 59% BFS) may result, at least in part, from the longer and more frequent follow-up that men with high diagnostic PSA, high pathologic Gleason sum, or high pathologic tumor stage experienced during the period studied. The nomogram significantly overestimated the disease-free progression rate for all 3 individual characteristics and the overall high-risk group. The analysis of the individual high-risk parameters was undertaken to determine what might be driving the difference between predicted and actual outcome among high-risk patients. The number of patients in each category are relatively low, so it is still unclear what parameter, if any, is driving the difference between predicted and actual, although the difference is largest among patients who had high pathologic tumor stage. These results suggest that clinicians should use the Kattan nomogram cautiously among high-risk patients, especially those with high pathologic tumor stage, and should expect a lower BFS than predicted by the Kattan nomogram.

A similar analysis was performed considering intermediate-risk patients (diagnostic PSA level >10 ng/mL but ≤20 ng/mL, pathologic Gleason sum =7, pathologic tumor stage =pT2b or pT2c, or overall intermediate risk, defined as ≤1 intermediate-risk parameter, but no high-risk parameters). As with the high-risk analysis, the numbers in each grouping were smaller, but the nomogram significantly overestimated the disease-free progression rate among the “any intermediate risk” group, as well as each of the individual intermediate-risk parameters. Although still significantly different, the differences between the means of each intermediate-risk grouping are less than those among the high-risk groupings. As with the high-risk analysis, the largest difference between predicted and actual BFS for intermediate-risk groups comes from patients with higher pathologic tumor stage. The relatively small differences between predicted and actual BFS for intermediate-risk patients suggests that clinicians can use the Kattan nomogram more confidently for intermediate-risk patients, although they should still expect a lower actual BFS than is predicted.

Like other validation studies using an independent group of patients who underwent RP, ^{9,11–16} this study showed that Kattan BCRFP nomogram predictions were robust for clinicians assessing the likelihood of BF and TF. The Kattan BCRFP nomogram predictions for this group of patients were more accurate than those of previous studies, especially the 10-year predictions. However, it should be noted that the 5-year BCRFP predictions among a subgroup of high-risk patients with at least 5 years of follow-up consistently overestimated actual 5-year BFS, which suggests that the Kattan nomogram should be used cautiously among this group. Five-year BCRFP predictions among a subgroup of intermediate-risk patients also overestimated actual 5-year BFS, but to a lesser degree than high-risk patients. Limitations of this study included the relatively low numbers of death from any cause (n=170; 9%), development of distant metastatic disease (n=74; 4%), or death from prostate cancer (n=24; 1%), despite the relatively long follow-up. These low numbers illustrate the relatively good prognosis for most patients with prostate cancer undergoing RP, and the relative difficulty in identifying which patients will experience clinically significant prostate cancer. Any study assessing disease risk should consider the development of distant metastatic disease or death from disease as treatment outcomes, but longer follow-up is required to assess these more clinically meaningful outcomes. Almost all patients with prostate cancer develop BF or TF on their way to metastatic disease. However, BF, TF, and

the Kattan BCRFP nomogram are not indicators for the development of distant metastatic prostate cancer, or prostate cancer death, because not all BF or TF patients develop metastasis. Other limitations to this work include difficulty recognizing the potential effects of (1) differences among surgeons; (2) robotic RP replacing open RP at RPCI; (3) increased PSA sensitivity; (4) modifications to the staging system; and (5) lack of a standardized definition for TF.

Conclusions

The Kattan BCRFP nomogram is a robust predictor of NCCN outcomes in a large sample of patients who underwent RP with a substantial follow-up duration. The predictions for BCRFP at 10 years, in particular, very nearly match actual outcomes for BFS. The Kattan BCRFP nomogram is a useful and accurate tool for assessing risk among patients who have undergone RP.

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Figure 1. Biochemical recurrence-free progression (BCRFP) versus biochemical failure-free survival (BFS) at (A) 5 years and (B) 10 years.

Figure 2. Biochemical recurrence-free progression (BCRFP) versus treatment failure-free survival (TFS) at (A) 5 years and (B) 10 years.

Figure 3. Biochemical recurrence-free progression (BCRFP) and biochemical failure-free survival (BFS) at 5 years for high-risk patients. Abbreviation: PSA, prostate-specific antigen.

Figure 4. Biochemical recurrence-free progression (BCRFP) at 5 years and biochemical failure-free survival (BFS) at 5 years for intermediate-risk patients. Abbreviation: PSA, prostate-specific antigen.

Table 1

Patient Characteristics

Characteristic	N	%
Age at RP, y		
<45	14	1
45–54	353	18
55–59	474	25
60–64	466	24
65–74	609	32
75	15	1
Race		
European American	1,741	90
African American	152	8
Other	38	2
Diagnostic PSA, ng/mL		
<4	385	20
4–10	1,273	66
10–20	197	10
>20	76	4
Clinical Gleason sum		
<7	938	49
7 (3+4)	527	27
7 (4+3)	250	13
>7	202	10
Missing	14	1
Clinical stage		
T1a/T1c	1,188	62
T2a/T2b/T2x	517	27
T2c	133	7
T3a/T3b/T4/T1b	70	4
Missing	23	1
Pre-RP NCCN recurrence risk categories ¹⁷		
Low	704	36
Intermediate	885	46
High	317	16
Very high	25	1
Pathologic Gleason sum		
<7	601	31
7 (3+4)	808	42
7 (4+3)	327	17

Characteristic	N	%
>7	195	10
Pathologic stage		
T2a/T2b/T2x	232	12
T2c	1,050	54
T3a	450	23
T3b	152	8
T4	47	2
Positive surgical margin	489	25
Lymph nodes at RP		
Not assessed	788	41
Negative	1,101	57
Positive	42	2
Neoadjuvant ADT		
No	1,789	93
Yes	142	7
Outcomes		
Biochemical failure	412	21
Treatment failure	480	25
Distant metastatic prostate cancer	55	3

Abbreviations: ADT, androgen deprivation therapy; PSA, prostate-specific antigen; RP, radical prostatectomy.

Table 2

Summary of Validation Studies for Kattan BCRFP (or Postoperative) Nomogram

Author/Reference	Study Type	Patients Studied	Year of Surgery	Failure Definition	Mean Follow-Up	Range Follow-Up	Result
Kattan et al, ¹¹ 1999	Training and validation	996 for training; 322 for validation	1990–1997	PSA >0.4 ng/mL + confirming value OR TF	37 mo	0–168 mo	Area under ROC curve =0.89
Graefen et al, ¹⁴ 2002	Validation with groups from 4 different institutions	2,465	1987–2000	Depends on institution	26.5 mo	NA	Area under ROC curve =0.80
Bianco et al, ¹³ 2003	Validation, compare predictions for African Americans and Caucasian Americans	1,043 (721 Caucasian Americans; 333 African Americans)	1990–1999	PSA >0.4 ng/mL and increasing	51 mo (for patients without recurrent or residual disease)	7–145 mo	Concordance index for Caucasian Americans =0.85; concordance index for African Americans =0.83
Stephenson et al, ⁹ 2005	Training and validation	1,881 for training; 1,782 for validation set #1; 1,357 for validation set #2	1983–2003	PSA >0.2 ng/mL + confirming value OR received treatment >12 mo after RP	40 mo (validation set #1); 53 mo (validation set #2)	1–164 mo	Concordance index =0.81 for validation set #1; concordance index =.77–0.78 for validation set #2
Kattan et al, ¹⁶ 2009	Validation with groups from 4 different institutions	7,724	1987–2003	PSA >0.4 ng/mL and increasing OR TF	47 mo (without recurrence)	0–156 mo	Concordance index =0.812
Swanson et al, ¹² 2011	Training and validation	1,881 for training; 684 for validation	1985–1995	PSA >0.2 ng/mL	85 mo	0–213 mo	Concordance index =0.7859
Cho et al, ¹⁵ 2014	Validation with Korean group	295	1994–2003	PSA 0.2 ng/mL	45 mo	1–148 mo	C statistic =0.76
Present study	Validation	1,931	1993–2014	Biochemical failure; TF	54 mo	0–244 mo	Area under ROC curve =0.772 (BFS); ROC =0.774 (TFS)

Abbreviations: BCRFP, biochemical recurrence-free progression; BFS, biochemical failure-free survival; NA, not applicable; PSA, prostate-specific antigen; ROC, receiver operating characteristic; RP, radical prostatectomy; TF, treatment failure; TFS, treatment failure-free survival.