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CME ARTICLE

PRETREATMENT NOMOGRAM FOR PREDICTING FREEDOM FROM RECURRENCE AFTER PERMANENT PROSTATE BRACHYTHERAPY IN PROSTATE CANCER

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ABSTRACT

Objectives. To develop a prognostic nomogram to predict the freedom from recurrence for patients treated with permanent prostate brachytherapy for localized prostate cancer.

Methods. We performed a retrospective analysis of 920 patients treated with permanent prostate brachytherapy between 1992 and 2000. The clinical parameters included clinical stage, biopsy Gleason sum, pretreatment prostate-specific antigen (PSA) value, and administration of external beam radiation. Patients who received neoadjuvant androgen deprivation therapy were excluded. Failure was defined as any post-treatment administration of androgen deprivation, clinical relapse, or biochemical failure, defined as three PSA rises. Patients with fewer than three PSA rises were censored at the time of the first PSA rise. Data from two outside institutions served as validation.

Results. A nomogram that predicts the probability of remaining free from biochemical recurrence for 5 years after brachytherapy without adjuvant hormonal therapy was developed using Cox proportional hazards regression analysis. External validation revealed a concordance index of 0.61 to 0.64, and calibration of the nomogram suggested confidence limits of +5% to −30%.

Conclusions. The pretreatment nomogram we developed may be useful to physicians and patients in estimating the probability of successful treatment 5 years after brachytherapy for clinically localized prostate cancer. UROLOGY **58:** 393–399, 2001. © 2001, Elsevier Science Inc.

Prognostic nomograms, which predict probabilities of freedom from progression, have been developed for patients treated with surgery and radiotherapy for clinically localized prostate cancer.[1–3] One advantage of the nomogram paradigm for predicting cancer control is that it models risk on a continuous scale rather than classifying patients into discrete risk groups. Risk groups are inherently heterogeneous and tend to predict outcomes less accurately than continuous models.[1] Thus, nomograms may be particularly helpful for physicians and patients discussing therapy, planning treatment, and developing prospective trials.

Outcome predictions for patients treated with permanent prostate brachytherapy using the modern transperineal approach are less common than predictions for surgery or radiotherapy. Some studies have presented results using different definitions of success,[4–6] and even fewer have attempted to stratify patients by risk to predict biochemical freedom from recurrence.[7–10] As identified in both the surgery and radiotherapy nomograms, a prostate-specific antigen (PSA) value of 3.0 ng/mL may predict a different outcome than a value of 9.9 ng/mL, even when the other variables are identical. Grouping patients is an inefficient use of data, as patients in one stratum are ignored when predicting the outcome for another stratum, even though the two strata may share certain characteristics. This loss of predictive accuracy identifies the weakness of this type of stratification scheme. The purpose of the present study was to

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TABLE I. ***Patient characteristics from the three contributing centers***

	MSKCC at Mercy Medical Center (n = 920)	Seattle Prostate Institute (n = 1827)	Arizona Oncology Services (n = 765)
Biopsy Gleason sum (n)			
2	7 (0.8)	31 (1.7)	16 (2.1)
3	31 (3.4)	86 (4.7)	42 (5.5)
4	37 (4.0)	352 (19.3)	69 (9.0)
5	80 (8.7)	449 (24.6)	140 (18.3)
6	486 (52.8)	563 (30.8)	367 (48.0)
7	243 (26.4)	279 (15.3)	108 (14.1)
8	36 (3.9)	67 (3.7)	23 (3.0)
Clinical stage (n)			
T1c	465 (50.5)	598 (32.7)	140 (18.3)
T2a	407 (44.2)	1118 (61.2)	530 (69.3)
T2b	48 (5.2)	111 (6.1)	95 (12.4)
External beam (n)			
No	756 (82)	1376 (75.3)	715 (93.5)
Yes	164 (18)	451 (24.7)	50 (6.5)
Pretreatment PSA (ng/mL)			
Minimum	0.6	0.2	0.1
1st quartile	5.7	5.0	5.1
Median	8	7.6	7.4
Mean	10	9.6	9.8
3rd quartile	11.5	11.1	10.9
Maximum	112	96.9	92
Follow-up			
Biochemical relapse	110	137	106
Clinical relapse	3	64	46
Hormonal therapy	9	4	34
Salvage prostatectomy	2	0	0
Death from disease	0	0	1
None (censored)	796	1622	578
Median (maximal) follow-up for censored patients (mo)	29 (88)	34 (121)	22 (114)

KEY: MSKCC = Memorial Sloan-Kettering Cancer Center; PSA = prostate-specific antigen.
Numbers in parentheses are percentages, unless otherwise noted.

develop a nomogram, using continuous risk estimation modeling, to predict the probability of remaining free from biochemical recurrence for 5 years in patients with clinical Stage T1-2 prostate cancer treated by permanent prostate brachytherapy.

MATERIAL AND METHODS

Three treatment centers (Memorial Sloan-Kettering Cancer Center at Mercy Medical Center, Seattle Prostate Institute, and Arizona Oncology Services) supplied clinical and raw follow-up data on their brachytherapy patients. The Memorial Sloan-Kettering Cancer Center at Mercy Medical Center data set was used to develop the nomogram, and the other two data sets were used for validation. Each center used similar treatment protocols and techniques and published its data separately.[11–13] The descriptive clinical statistics appear in Table I. All patients treated with neoadjuvant hormones were excluded. The 1997 TNM clinical staging system was used.[14] Because of small numbers, patients with clinical Stage T1a, T1b, or T3 cancers or biopsy Gleason sums greater than 8 were excluded, as were patients with pretreatment PSA levels higher than the maximal value observed at Memorial Sloan-Kettering Cancer Center at Mercy Medical Center. We chose as predictors variables that were both commonly available and theoretically predictive of outcome. No variable selection procedures were used.

All actual follow-up PSA values were provided from each center to allow for a standardized definition of PSA failure across the treatment cohorts. The American Society for Therapeutic Radiology and Oncology (ASTRO) definition of PSA failure after external beam radiotherapy was applied in this study.[15] This definition marks failure at the midpoint in time between the post-treatment nadir and the first of three consecutive PSA rises. However, two important conservative modifications were made.[16] First, the requirement that the three rises must be consecutive was relaxed. If three rises occurred with intervening stable PSA values, but the PSA level never decreased, the treatment for that patient was considered a failure at the midpoint in time between his first rise and the PSA level immediately before the first rise. This identification represents an increase in sensitivity over the ASTRO definition, which determines failure only when the rises are consecutive. Second, for patients whose most recent PSA values were rising at the time of their last follow-up, but in whom failure had not occurred, the follow-up time was truncated at the PSA level

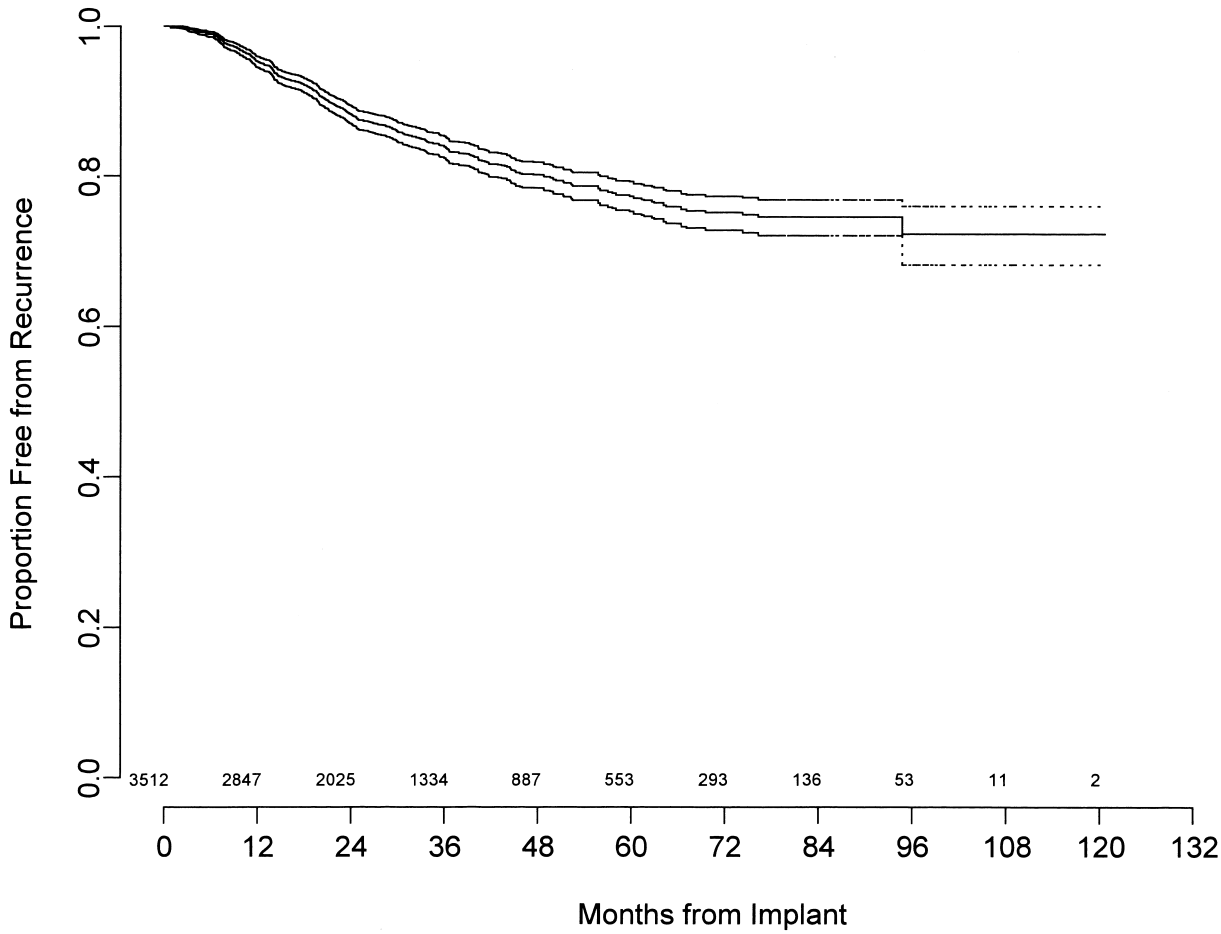


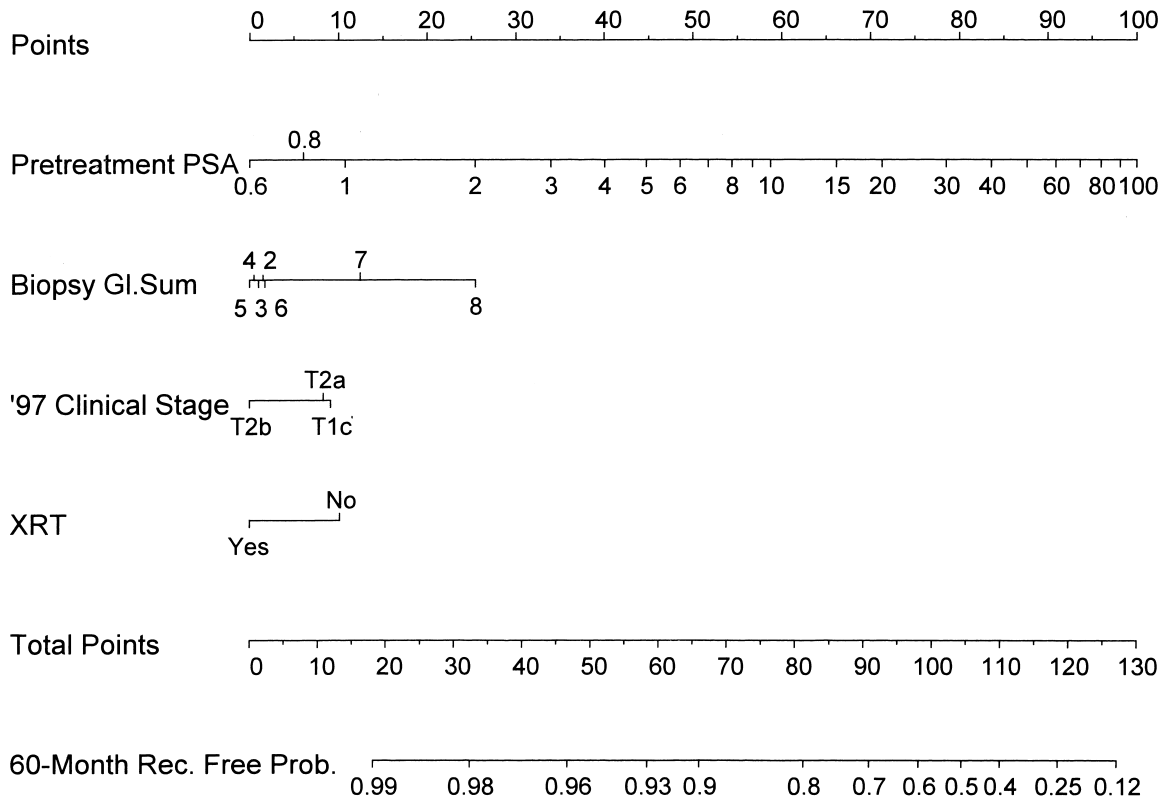
FIGURE 1. *Kaplan-Meier estimates of disease-free probability with 95% confidence bands for all cohorts combined (n = 3512). Numbers above the months indicate patients at risk of recurrence. Although many of the failures were observed before 60 months, recurrence beyond this point did occur.*

immediately before the first rise. This technique reduced the "backdating" problem associated with the ASTRO definition, whereby patients are currently judged to be disease free but later declared to have treatment failure at a prior date. With this early censoring adjustment, patients with equivocal PSA values were not considered disease free beyond the time of the nadir PSA value, as they would be with the ASTRO definition. The net effect of these modifications was to increase the number of treatment failures and to reduce the survival time granted to the censored patients, both of which lowered the freedom from recurrence curve.[16] Clinical relapse, death from disease, and secondary treatments were also considered treatment failures if they occurred before a PSA failure (Table I).

The nomogram was developed using a Cox proportional hazards regression model. The predictor variables were pretreatment PSA, clinical stage, biopsy Gleason sum, and whether external beam radiotherapy was administered. To accommodate for potential nonlinear effects, restricted cubic splines were used for the pretreatment PSA, which was log transformed. Second and third order interactions were explored, and the proportional hazards assumption was verified. Two methods of validation were used. First, discrimination was quantified with the concordance index,[17] a measure similar to an area under the receiver operating characteristic curve but appropriate for censored data.[18] Second, the calibration was examined by plotting the predictions made by the nomogram against the actual freedom from biochemical recurrence, which were measured by the Kaplan-Meier method. Both discrimination and calibration were performed using the two separate validation data sets. All analyses were performed using S-Plus 2000 software (Mathsoft) incorporating the Design and Hmisc libraries.[19]

RESULTS

The Kaplan-Meier freedom from recurrence curve for the combined data sets is shown in Figure 1. The potential differences among the individual series in the Kaplan-Meier plots would not necessarily be relevant, because baseline imbalances in the prognostic factors may explain the different outcome rates. PSA ($P = 0.0001$), biopsy Gleason sum ($P = 0.0003$), and adjuvant radiotherapy ($P = 0.0487$) were independent predictors of freedom from recurrence in the Cox regression model, and clinical stage ($P = 0.5344$) was not. No violation in the proportional hazards assumption was seen ($P = 0.66$), and no second or third order interactions occurred at the 5% level of significance. The nomogram from this Cox model appears in Figure 2.



Instructions for Physician: Locate the patient's PSA on the **Pretreatment PSA** axis. Draw a line straight upwards to the **Points** axis to determine how many points towards recurrence the patient receives for his PSA. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to find the patient's probability of remaining recurrence free for 60 months assuming he does not die of another cause first.

Note: This nomogram is not applicable to a man who is not otherwise a candidate for permanent prostate brachytherapy. You can use this only on a man who has already selected permanent prostate brachytherapy as treatment for his prostate cancer. You must decide upon use of adjuvant XRT prior to consulting this nomogram.

Instruction to Patient: "Mr. X, if we had 100 men exactly like you, we would expect between <predicted percentage from nomogram – 30%> and <predicted percentage + 5%> to remain free of their disease at 5 years following permanent prostate brachytherapy, and recurrence after 5 years is very rare."

FIGURE 2. *Nomogram for predicting 5-year freedom from PSA recurrence after permanent prostate brachytherapy without neoadjuvant androgen ablative therapy.*

When applied to the validation data sets, the concordance indexes were 0.61 (Seattle Prostate Institute) and 0.64 (Arizona Oncology Services). The calibration of the nomogram when applied to the validation data sets appears as Figure 3.

COMMENT

The techniques for transperineal permanent prostate brachytherapy are relatively modern, having been developed within the past 10 to 12 years, and the selected cohorts for this study represent some of the largest series with long follow-up. Compared with others who have tried to stratify patients treated with localized prostate cancer by discrete risk groups,[7,8] our nomogram instead provides continuous probabilities of freedom from recurrence for 5 years.

As a measure of nomogram discrimination, the concordance index ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). The nomogram developed here performs near the lower end of this scale, discriminating significantly better than chance ($P < 0.0001$), but not as well as the surgery[2] or external beam radiotherapy[1] nomograms, which had concordance indexes near 0.75. There may be several reasons for the apparent inaccuracy. The data used in this study were retrospective consecutive cases performed during the complete time spectrum of this procedure. The technical improvements and changes in technique have been numerous and influential during this period and likely affect the results. Such changes in technique cannot be examined in these data sets. However, the year of implant was not a significant

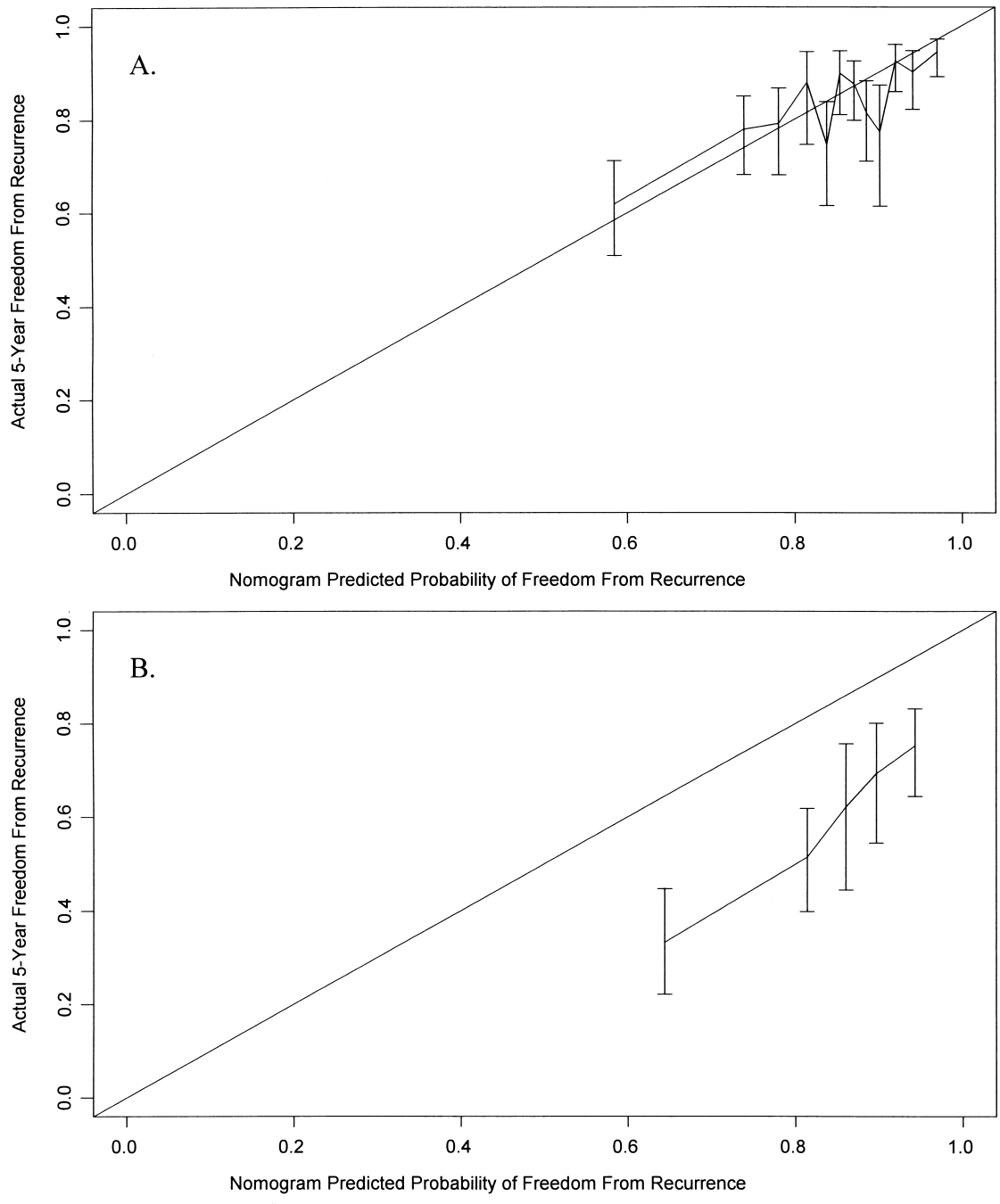


FIGURE 3. *Calibration curves for the validation cohorts. (A) Seattle Prostate Institute. (B) Arizona Oncology Services. The x-axis represents nomogram predictions. The y-axis is the actual 5-year freedom from recurrence using the Kaplan-Meier method. Each point represents a subcohort of approximately 150 patients; the vertical bands are 95% confidence intervals.*

predictor of outcome in the multivariate analysis. Also, the maximum biopsy Gleason sum used from these data was 8, and the primary and secondary grades were not distinguished; the updated 1997 TNM staging system combines the 1992 T2a and T2b clinical stages into a single category (T2a); and patients with clinical Stage T3 were excluded. Thus, the biopsy Gleason sum and clinical stage predictor variables were compressed relative to those used in the surgery and radiotherapy nomograms. This may be hampering the ability of the brachytherapy nomogram to discriminate, since the patients would be more homogenous. Furthermore, PSA was not measured in a central laboratory, which may negatively affect its predictive value. Similarly, the Gleason sums were not assigned by a single study pathologist, and it is not clear whether imaging was used to assign patients

to Stage T2 cancer or substages within T2 cancer. Nomogram prediction may be improved with the addition of variables obtained from the analysis of systematic biopsy data, such as the percentage of positive cores. These data were available from only one of the three centers, so we were unable to examine their impact.

Nomogram calibration (Fig. 3) suggests outcome differences among the centers, which were incorporated into the text of our nomogram. The calibration curves suggest that the outcome probabilities may be as much as 5% better or 30% worse than that predicted by the nomogram, so this is part of the instructions in the nomogram legend. Strangely, the institution with the lower concordance index appeared to have better calibration accuracy (Fig. 3A). Such a level of accuracy calls into question the usefulness of this nomogram. Answering this question requires consideration of the alternative. One alternative is to simply quote the overall freedom from recurrence probability from a long-term study such as that of Ragde *et al.*[20] There are two concerns with this option. First, the method used to compute the freedom from recurrence in that study was not the standard Kaplan-Meier or cumulative incidence estimators. Instead, it was a method that does not have as clear interpretability, as it does not appear to appropriately consider censored patients. In this regard, our Figure 1 is a preferred overall guide to long-term follow-up. Second, the nomogram in Figure 2 does predict better than the overall mean ($P < 0.0001$), which has no discriminating ability. Therefore, although imperfect, this nomogram may be better than any presently available alternative, short of no prediction at all.

In addition to serving as a prognostic tool, the nomogram in Figure 2 is also useful in interpreting the underlying Cox regression model. Interestingly, the effect of clinical stage in the nomogram was counterintuitive, with patients with Stage T1c disease apparently faring worse than those with Stage T2 disease. However, when interpreting the nomogram, it is essential to consider the possible changes in the other variables when comparing points across levels of a single variable. It is difficult to draw meaningful conclusions about the effect of a single variable in isolation when the other variables of the nomogram may correlate with it, since moving a patient on one axis (eg, clinical stage) would likely affect his position on the other axes (eg, PSA). Furthermore, it is important to consider that clinical stage was statistically insignificant, such that T2b disease, on average, was not shown to be worse than T1c disease. At first, the reaction to this finding was to delete clinical stage from the statistical model and nomogram. However, two problems would result. First, the prediction accuracy would be expected to actually decrease if the clinical stage were removed, as this is effectively a form of backward elimination, whereby the remaining variables have their effects overstated. Second, the confidence intervals would become falsely narrow, overstating the apparent accuracy of the nomogram. Therefore, the clinical stage was retained in the nomogram.

The reason for the graphical depiction of the nomogram in Figure 2 is one of accuracy. We plan to facilitate the computations of the nomogram by adding it to a nomogram Palm application called Prostogram, which we distribute free of charge at www.nomograms.org.

The potential applications for nomograms such as the one developed in the present study are multiple.[2,3] A patient weighing the risks and benefits of brachytherapy might benefit from the most accurate predictions of freedom from recurrence currently available. It should be emphasized that the development of the present nomogram was based on a cohort of patients treated with brachytherapy. Both physician and patient biases unquestionably affected the selection of treatment in this group of patients, as is the case for both the surgical and the radiotherapy nomograms. For example, obstructive symptoms may be an important prognostic factor for brachytherapy patients as it is for surgery patients,[21] and these patients may have been discouraged from brachytherapy. Certainly, a randomized trial would yield valuable data for modeling prognosis. Moreover, the data sets were from three very high-volume brachytherapy centers with considerable experience. Hence, the nomogram may not be entirely applicable to the general population of patients with localized prostate cancer and technically is only applicable to the patient who has already chosen brachytherapy. The role of all the pretreatment nomograms will be better defined as a component of a larger decision analysis[22] that incorporates individual patient preferences into the decision-making process.

The design of clinical trials may represent another application for nomograms. By quantifying the probability of treatment failure, prognostic nomograms identify patients most likely to benefit from neoadjuvant or adjuvant treatments. The selection of candidates would be facilitated by specifying a risk cutoff (eg, at least a 50% chance of treatment failure) rather than by risk stratification, which may not as easily produce homogenous groups of patients.[1]

In conclusion, a nomogram that predicts the 5-year outcome after permanent prostate brachytherapy for localized prostate cancer was developed and has a concordance index between 0.61 and 0.64. It may be a beneficial tool for physicians and patients as a part of the decision-making pro-

cess before brachytherapy for localized prostate cancer, and in identifying patients at high risk of failure after brachytherapy who may benefit from adjuvant treatment protocols.

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