Original Article

Outcomes After Prostate Brachytherapy Are Even Better Than Predicted

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BACKGROUND: During the first 3 years after prostate cancer treatment with radiation therapy, benign prostate-specific antigen (PSA) bounces are difficult for clinicians to distinguish from a biochemical recurrence, which can result in unnecessary interventions and erroneous predictions of outcomes. The objective of this study was to evaluate a commonly used PSA failure definition in a multinational, multi-institutional study after monotherapy with prostate brachytherapy. **METHODS:** Participants were selected from 2919 men who underwent permanent prostate brachytherapy at the University Medical Center Utrecht, Princess Margaret Hospital, or Seattle Prostate Institute between 1998 and 2006. Inclusion required not having received androgen-deprivation therapy and having at least 30 months of follow-up. Failure was defined as any post-treatment use of hormone therapy, clinical relapse, or prostogram-defined biochemical (PSA) failure. Cases in which the nomogram predicted biochemical failure were evaluated at each institution to verify biochemical status over time and the actual clinical outcome at 5 years. **RESULTS:** The median follow-up for the 1816 patients was 5.2 years. Concordance between the prostogram-predicted and actual outcomes, as measured by the Harrell *c* statistic, was 0.655 (95% confidence interval [CI], 0.536-0.774; $P = .010$) for the Princess Margaret group, 0.493 (95% CI, 0.259-0.648; $P = .955$) for the Seattle group, and 0.696 (95% CI, 0.648-0.744, $P < .001$) for the Utrecht group. The overall mean difference in biochemical recurrence-free survival at 5 years between actual outcomes and prostogram-defined outcomes was 9.2% (95% CI, 7.7%-10.6%). The total numbers of prostogram-defined and actual biochemical failures were 312 and 157, respectively ($P = .001$). **CONCLUSIONS:** The widely used prostogram could not adequately distinguish a benign PSA bounce from a biochemical recurrence after prostate brachytherapy and could not be used to counsel patients about their predicted outcomes after treatment. The authors conclude that, to avoid unnecessary active interventions after treatment, clinicians should monitor PSA levels for at least 3 years and provide reassurance to patients that a PSA rise during this time is common and may not indicate a treatment failure. ***Cancer* 2011;000:000–000.** © *2011 American Cancer Society.*

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INTRODUCTION

Prostate cancer is the most common cancer in men, and more than 200,000 new cases are diagnosed each year in the United States.[1] Upon diagnosis, men with prostate cancer are faced with deciding among several standard-of-care treatment options, which, depending on the disease stage at presentation, can include active surveillance, surgery, external-beam radiotherapy, and brachytherapy.[2] To aid in the decision process, several algorithms or nomograms have

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Steven J. Frank conceived and designed the study, drafted the article, and supervised the study; Lawrence B. Levy analyzed and interpreted the data and critically revised the article; Marco van Vulpen, Juanita Crook, John Sylvester, and Peter Grimm were responsible for data acquisition and critically revised the article; and David A. Swanson conceived and designed the study and critically revised the article. Steven J. Frank had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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been developed to compare the likelihood of disease progression after various types of treatment for newly diagnosed prostate cancer. One such nomogram in wide use[3] was developed and validated by Kattan and colleagues at the Memorial Sloan-Kettering Cancer Center. The simplicity of nomograms, which are freely available online, makes them attractive for clinicians and patients, because an individual's probability of progression-free survival after surgery, external-beam radiotherapy, or brachytherapy can be generated and compared in a matter of seconds.[3]

However, nomograms can be misleading if their predicted outcomes are incorrect. If patients are erroneously led to believe that their potential for cure is lower with 1 modality versus another, then they cannot reasonably compare those modalities in terms of their potential side effects, which can substantially affect quality of life and overall satisfaction after treatment. For example, radiotherapy generally is associated with more urinary bother (eg, frequency, urgency, hesitancy) and bowel symptoms, whereas surgery tends to be associated with problems with urinary incontinence and erectile dysfunction.[4,5] A previous analysis at The University of Texas MD Anderson Cancer Center demonstrated discordance between outcomes predicted by the Kattan nomogram (nicknamed the "prostogram") and actual outcomes after prostate brachytherapy: actual outcomes were superior to those predicted, and the predictive accuracy of the prostogram was low at <50%.[6] However, that study was criticized for its focus on patients with relatively low-risk disease who had been treated at a single high-volume institution. To answer those criticisms, we undertook the current study to validate the MD Anderson Cancer Center findings and to evaluate a commonly used PSA failure definition in a multinational, multi-institutional study after monotherapy with prostate brachytherapy.

MATERIALS AND METHODS

Study Populations

Institutional review board approval was obtained for this study at MD Anderson Cancer Center and at each of the 3 institutions that contributed patients for this analysis: the Princess Margaret Hospital in Toronto, Canada; the Seattle Prostate Institute in Seattle, Washington; and the University Medical Center Utrecht in the Netherlands. Patients were selected from a total of 2919 patients who were identified retrospectively as having undergone prostate brachytherapy since 1998 (1117 patients from University Medical Center Utrecht [1998-2006], 914 patients from Princess Margaret Hospital in Toronto [1999-2006], and 888 patients from the Seattle Prostate Institute [1998-2000]). The starting date of 1998 was chosen on the basis of a sentinel article by Stock and colleagues, published early that year, that defined appropriate dosimetric guidelines for the delivery and verification of appropriate radiation doses from implantation-based brachytherapy.[7] Exclusion criteria were receipt of hormone therapy before brachytherapy (which also was an exclusion criterion for the data sets that were used to derive the nomogram) and having at least 30 months of follow-up, resulting in a final cohort of 1816 patients (683 from Toronto, 731 from Utrecht, and 402 from Seattle).

Definitions of Outcome

Recurrence was defined as clinical relapse, death from disease, secondary treatments administered before a rise in serum prostate-specific antigen (PSA), any receipt of androgen-deprivation therapy after treatment, or biochemical evidence of recurrence according to the prostogram modification of the American Society for Therapeutic Radiation Oncology (ASTRO) definition of biochemical recurrence after external-beam radiotherapy. In other words, patients who had a total of 3 increases in serum PSA levels (with or without stable intervening PSA levels) and no PSA decreases were considered to have had a biochemical recurrence. According to the prostogram, for those patients who had had 1 or more PSA increases but did not meet the definition of 3 rises at last follow-up, the follow-up was truncated at the PSA measurement immediately before the first increase. For each patient who experienced biochemical recurrence according to the modified prostogram definition, that patient's clinical course was examined by the principal investigator from each institution. If the patient had had a PSA increase followed by a subsequent decrease in PSA in the absence of any intervention (ie, a "PSA bounce"), had received no salvage therapy, and had no evidence of disease at the time of analysis, then the "actual outcome" was coded as free of biochemical recurrence (ie, not failure). Our analyses in this report included both of these definitions of failure, the "prostogram-defined outcome" and the "actual outcome," as described below.

Data Analysis

The accuracy of the nomogram was assessed by comparing the probability of recurrence predicted by the

Table 1. Patient Characteristics

Characteristic	Contributing Institution: No. of Patients			
	Princess Margaret Hospital (n = 683)	University Medical Center Utrecht (n = 731)	Seattle Prostate Institute (n = 402)	Totals (n = 1816)
Gleason sum score				
2	0	4	1	5
3	1	5	3	9
4	2	61	13	76
5	12	254	47	313
6	619	257	230	1106
7	49	146	96	291
8	0	4	12	16
Clinical disease stage				
T1c	450	486	254	1190
T2a	231	187	110	528
T2b	2	58	38	98
External beam radiotherapy received				
Yes	29	0	101	130
No	654	731	301	1686
Pretreatment PSA level, ng/mL				
Minimum	0.3	1.0	0.4	
Median	5.4	8.3	6.2	
Mean	5.6	10.3	7.1	
Maximum	18.4	100.0	40.0	

Abbreviations: PSA, prostate-specific antigen.

nomogram with actual disease progression. The prostogram (SAS software, version 9.1.3; SAS Institute, Cary, NC) was used to calculate the 5-year probability of biochemical recurrence-free survival (BRFS) for each patient. Variables that were entered into the nomogram were pretreatment PSA level, Gleason sum score, the 1997 American Joint Committee on Cancer (AJCC) clinical tumor classification, and whether the patient had received external-beam radiotherapy in addition to brachytherapy.

Concordance between the probability of BRFS predicted by the prostogram and the actual recurrence rate was assessed by using the Harrell *c* statistic based on the Kattan recurrence criterion (3 consecutive PSA increases with no decreases), which was calculated with the function "rcorr.cens" from the Hmisc library[8] in the R statistical software package (version 2.6.1; The R Foundation for Statistical Computing, Vienna, Austria). This is the same statistical tool that was used to evaluate the original prostogram.[8,9] Patients were then grouped into quartiles based on the 5-year BRFS probability as predicted by the prostogram. For each quartile, the mean of the predicted probabilities was compared with the mean of the actual 5-year BRFS rate. Outcomes according to the definition of biochemical failure within the prostogram ("prostogram-defined outcomes") were then compared with the actual outcomes. The differences in freedom from failure at 5 years (the proportion of actual failures minus the proportion of prostogram-defined failures), with 95% confidence intervals (CIs), were calculated based on 10,000 bootstrap samples.

RESULTS

Patient Characteristics

Characteristics of the 1816 patients comprising the validation cohort are listed in Table 1. The median follow-up for the entire cohort was 62.5 months (range, 30.0-127.0 months); the median follow-up for the institutional subgroups was 55.2 months (range, 30.2-113.2 months) for the Toronto patients (n = 683), 60.0 months (range, 30.0-127.0 months) for the Utrecht patients (n = 731), and 86.1 months (range, 30.4-114.8 months) for the Seattle patients (n = 402). Patients who received brachytherapy at Utrecht had higher pretreatment PSA levels, disease stage, and Gleason sum scores ($P < .001$). Patients who were treated at Seattle were more likely to have received combination therapy (brachytherapy with external-beam radiotherapy; $P < .001$) than patients who were treated at the other 2 centers.

Concordance Between Prostogram-Predicted Outcomes, Prostogram-Defined Outcomes, and Actual Outcomes

The prostogram-predicted 5-year biochemical (PSA) control rate (ie, the freedom from biochemical recurrence rate) for the entire cohort of 1816 patients was 84.3%, and the corresponding rates for each institution were 88.5% for Toronto, 80.3% for Utrecht, and 84.3% for Seattle. Predicted outcomes were significantly worse for the Utrecht group, because the patients in that group presented with more advanced disease ($P < .0001$). Concordance of the prostogram-predicted outcomes with the prostogram-defined outcomes, as measured by the Harrell *c* statistic, was as follows: 0.531 (95% CI, 0.468-0.595; $P = .338$) for the Toronto group, 0.542 (95% CI, 0.455-0.630; $P = .346$) for the Seattle group, and 0.660 (95% CI, 0.617-0.702; $P < .001$) for the Utrecht group. In other words, the prostogram was not predictive of outcomes for the Toronto or Seattle groups. When actual outcomes were used instead of prostogram-defined outcomes, the concordance of the prostogram-predicted outcome with actual outcome, again measured with the Harrell *c* statistic, was as follows: 0.655 (95% CI, 0.536-0.774; $P = .010$) for the Toronto group, 0.493 (95% CI, 0.259-0.648; $P = .955$) for the Seattle group, and 0.696 (95% CI, 0.648-0.744; $P < .001$) for the Utrecht group. In other words, the predictive accuracy of the prostogram for the Seattle group was <50%. Concordance assessed in terms of numerical ranking did not correlate with actual outcomes, and concordance measured by the Harrell *c* statistic did not suggest accuracy of actual patient outcomes. The extent of discordance between numerical ranking and treatment outcomes is indicated because the actual progression-free rates were better than the prostogram-predicted probabilities for each quartile: 81.2% actual versus 71.5% predicted for the first quartile, 92.8% actual versus 84.1% predicted for the second quartile, 95.4% actual versus 88.4% predicted for the third quartile, and 97.8% actual versus 93% predicted for the fourth quartile. In other words, >50% of the prostogram-predicted "failures" were not actually failures, as described further below.

Extent of Difference in Prostogram-Defined Outcomes Versus Actual Outcomes

At 5 years, the overall mean difference in freedom from biochemical failure between the actual outcomes and the prostogram-defined outcomes for the entire cohort (n = 1816) was 9.2% (95% CI, 7.7%-10.6%) (Fig. 1A). The corresponding mean differences in freedom from biochemical failure at 5 years for each contributing institution were as follows: 10.9% (95% CI, 8.6%-13.5%) for the Toronto group (Fig. 1B), 6.2% (95% CI, 7.7%-10.6%) for the Utrecht group (Fig. 1C), and 11.9% (95% CI, 8.6%-15.6%) for the Seattle group (Fig. 1D). At 2 years, according to the prostogram's definition of failure, 204 patients would be considered to have experienced failure—but only 93 patients had actually developed biochemical failure. Therefore, at 2 years, more than half (54.4%) of the prostogram-defined biochemical failures were benign PSA bounces and not biochemical failures. The prostogram-defined failures versus actual failures at Princess Margaret Hospital in Toronto were 92 and 29, respectively ($P < .0001$); the rates at Utrecht were 173 and 134, respectively ($P < .001$); and the rates at Seattle were 47 and 3, respectively ($P < .0001$). The total number of prostogram-defined failures and actual biochemical failure were 312 and 157, respectively ($P = .001$); therefore 50.3% of the prostogram-defined failures were not biochemical failures. Figure 2A-C illustrates examples from each institution of changes in PSA levels over time that would indicate a prostogram-defined failure that was not a biochemical failure but simply a benign PSA bounce. At 3 years, 68 of 72 prostogram-defined failures in Toronto (94.4%) were benign PSA bounces; the corresponding numbers for Utrecht were 125 of 173 (72.3%), respectively, and those for Seattle were 36 of 47 (76.6%), respectively.

To account for the possibility that the prostogram-defined failures may have better correlation with patients exposed to hormone therapy, we also analyzed the prostogram-defined failures and the actual failures in all of the patients without excluding those who had received neoadjuvant hormone therapy or who had <30 months of follow-up. For the entire data set of 2919 patients, the actual rates of freedom from biochemical recurrence were 92% at 5 years and 90.4% at 10 years; the corresponding prostogram-defined outcomes were 82.1% at 5 years and 77.8% at 10 years ($P = .001$) (Fig. 3). According to the prostogram's definition of biochemical failure, 439 men experienced treatment failure; whereas the actual number of treatment failures was 201 ($P < .0001$). Therefore, 54% of the "failures" defined by the prostogram were not true biochemical failures. At 2 years, 308 patients had experienced biochemical failure according to the prostogram definition, whereas 129 patients actually did experience biochemical failure. Therefore, at 2 years, 58% of cases that were considered biochemical failures according

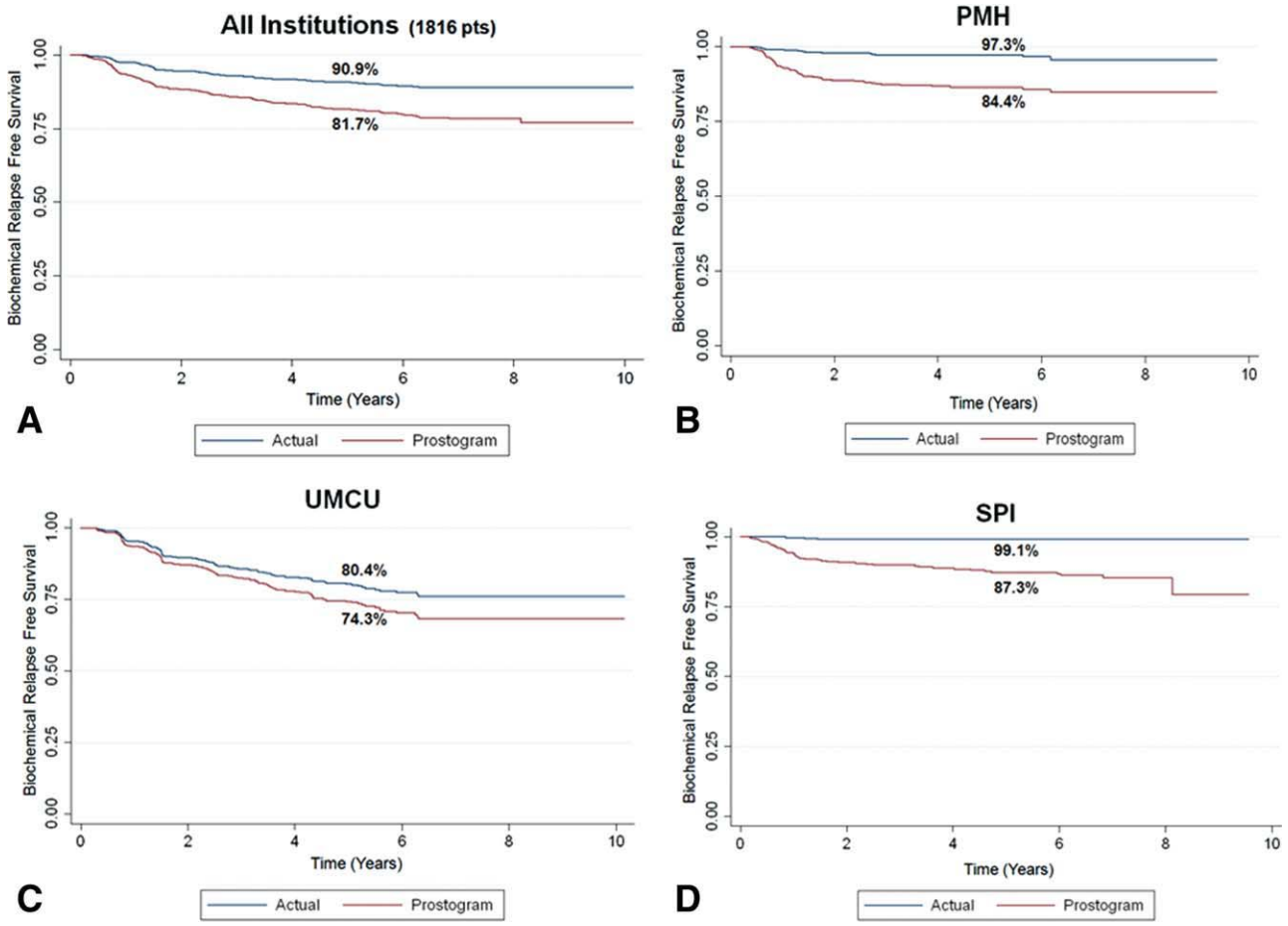

Figure 1. Freedom from biochemical failure survival rates are illustrated according to the prostogram definition and the actual outcomes after patients underwent iodine 125 or palladium 103 implantation-based brachytherapy at 1 of 3 treatment centers. Mean differences in predicted versus actual freedom from biochemical failure at 5 years are shown (A) for the entire group (n = 1816) and for patients who received treatment (B) at Princess Margaret Hospital (PMH) in Toronto (n = 683), (C) at the University Medical Center Utrecht (UMCU) in the Netherlands (n = 731), and (D) at the Seattle Prostate Institute (SPI) (n = 402).

to the prostogram definition were benign PSA bounces and, in fact, were not biochemical failures.

DISCUSSION

To our knowledge, this report represents the first multinational, multi-institution attempt to evaluate the predictive ability of the prostogram for men who received prostate brachytherapy, and the results challenge its usefulness as an accurate predictive clinical tool. Actual outcomes after prostate brachytherapy were better than the prostogram had predicted, in agreement with a previous report from MD Anderson Cancer Center.[6] The lack of accuracy after prostate brachytherapy results at least in part from the prostogram's definition of biochemical failure, which cannot distinguish a biochemical failure from a benign PSA bounce during the first 3 years after treatment. Consequently, >50% of the prostogram outcome "failures" were not clinical failures.

We observed that the prostogram lacked generalizability by not performing consistently when applied to multiple data sets from different institutions, and it was inaccurate when applied to those heterogeneous novel populations. The prostogram lacked discrimination by not accurately predicting which patients would have a biochemical relapse, and its generated predictions did not reflect actual outcomes. At 5 years, the rate of BRFS according to the prostogram definition was 9.2% higher than the actual recurrence-free rate at that time. For patients who present with localized disease that is amenable to brachytherapy, the implications from these findings are significant: First, until the prostogram can account for

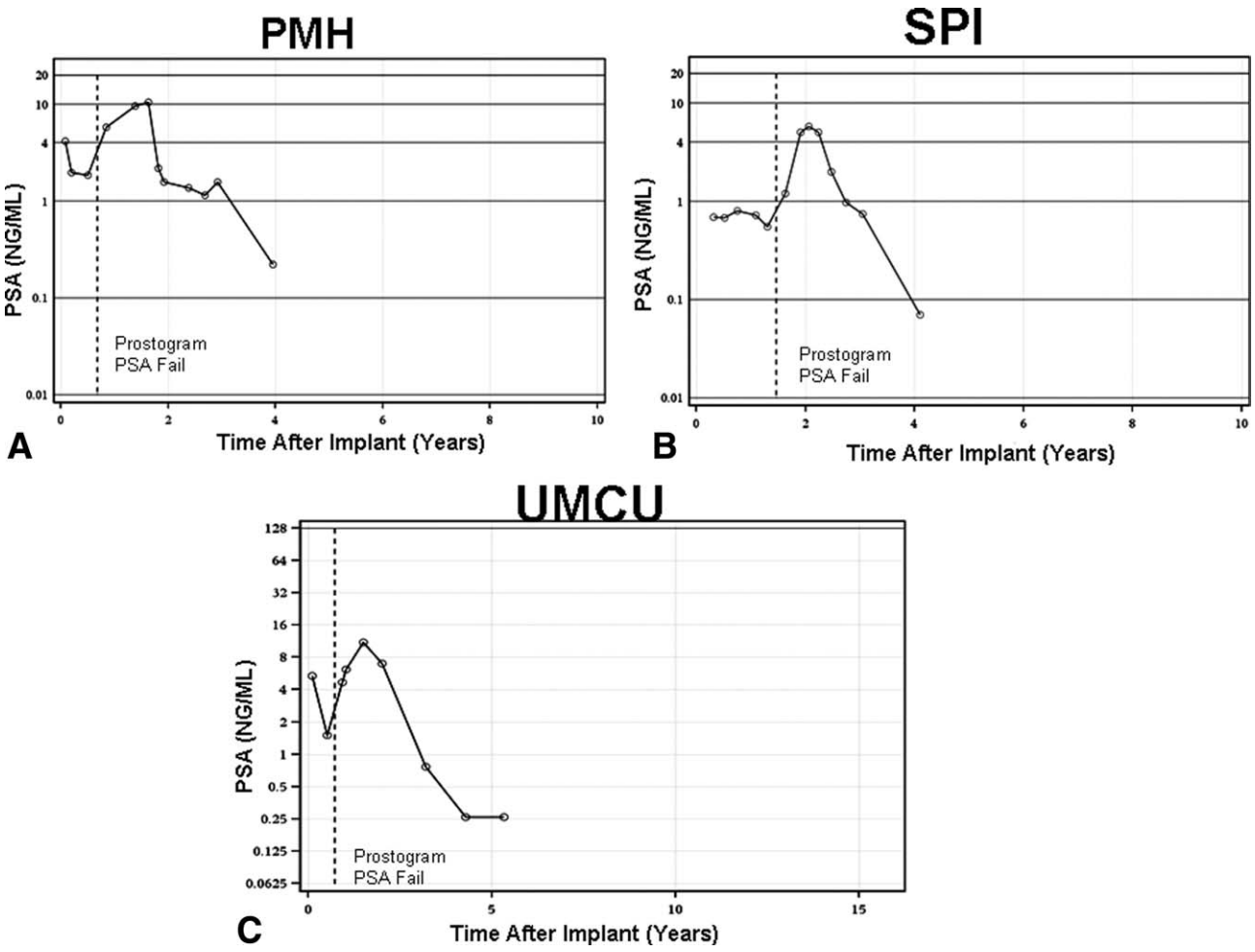

Figure 2. These plots illustrate serum prostate-specific antigen (PSA) levels (in ng/mL) over time for 3 patients, 1 from each participating institution, who would be defined as "biochemical failures" by the prostogram but who actually had benign PSA bounces, including (A) a patient from Princess Margaret Hospital (PMH) in Toronto, (B) a patient from the University Medical Center Utrecht (UMCU), and (C) the Seattle Prostate Institute (SPI).

the PSA bounce, it should not be used to counsel patients about predicted outcomes after brachytherapy. Second, because outcomes between treatment modalities are more similar than previously expected, patients who present with localized prostate cancer may be able to focus on quality-of-life outcomes and overall satisfaction after treatment in choosing which type of therapy to receive.

The pretreatment prostogram incorporates only 4 variables for predicting outcomes after brachytherapy: PSA level, 1997 AJCC clinical disease stage, Gleason sum score, and whether external-beam radiotherapy was used with the brachytherapy.[9,10] Subsequently, the 1997 AJCC clinical staging system was deemed inaccurate, and the sixth (2002) edition of the staging system was changed back to the 1992 AJCC system. Another potential problem may be that the Gleason sum score may not accurately predict the course of the disease, because the sum score does not reflect the dominant grade. In the prostogram formula, the pretreatment PSA level carries the largest weight in determining the predictive score. For a patient who has a PSA level of 8 ng/mL, clinical T1c disease, and 1 of 12 biopsy cores that are positive for Gleason 6 disease, the prostogram predicts that that patient's 5-year recurrence-free probability after brachytherapy is 84%.[3] This prediction is inaccurate; it is far poorer than the actual results reported at MD Anderson Cancer Center[6] and at each of the 3 institutions represented in the current study. Thus, if such a patient were to use the prostogram to guide treatment selection for localized disease, then that patient may be inclined to choose external-beam radiotherapy instead, for which the predicted 5-year BRFS is 90%, or radical prostatectomy, for which the corresponding 5-year

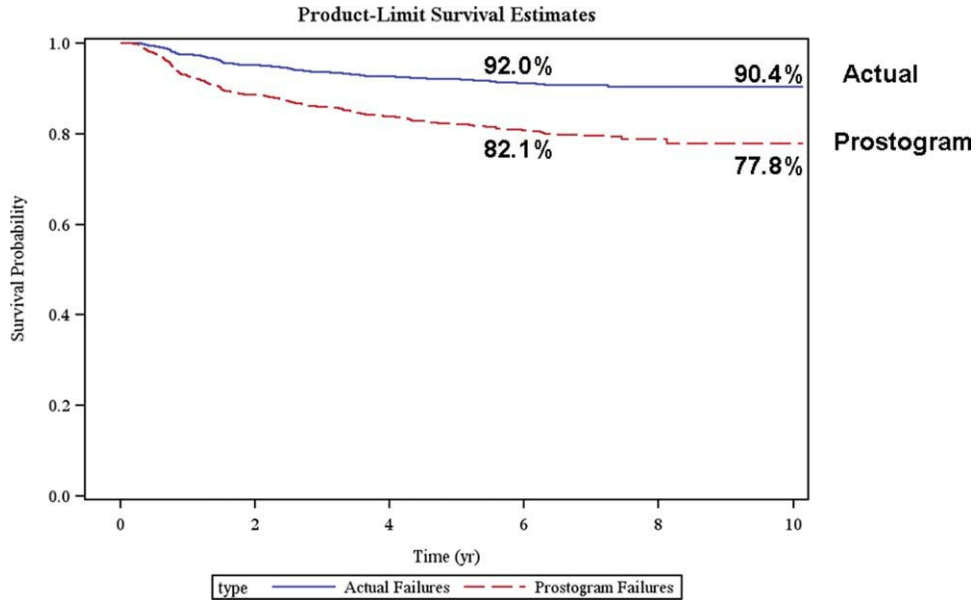

Figure 3. These are product-limit survival estimates of biochemical relapse-free survival according to the prostogram definition and the actual outcomes after brachytherapy for all 2919 patients (pts) from the 3 contributing institutions. Note that the inclusion of patients who received hormone therapy before brachytherapy or who had <30 months of follow-up did not improve the discrepancy between the 2 definitions of treatment failure.

BRFS is 98% and the 10-year BRFS is 96%. For such a patient, overall satisfaction and quality-of-life factors (ie, incontinence, rectal bleeding, and erectile dysfunction) may be subjugated to a perceived cure and guide him away from choosing brachytherapy.

In addition to possible shortcomings related to poor choice of predictive variables,[6] the overall inaccuracy of the prostogram can be directly linked to the definition of biochemical failure used within the prostogram and the benign PSA bounce phenomenon. The prostogram incorporated a modification of the ASTRO definition of biochemical recurrence after external-beam radiotherapy[10] in which having 3 PSA increases, with or without stable intervening PSA levels, and no PSA decreases was considered to represent biochemical recurrence. The nomogram inaccurately predicts treatment failure during the first 2 years after treatment because of the well reported benign phenomenon of the PSA bounce.[10] The prostogram was developed from data sets that were collected from 1992 through 2000 at 3 institutions: Seattle Prostate Institute, Arizona Oncology Services, and Memorial Sloan-Kettering Cancer Center at Mercy Medical Center. The corresponding median follow-up at each institution was 34 months, 22 months, and 29 months, respectively.[9] The benign PSA bounce phenomenon had not been fully appreciated when the prostogram was first validated and described by Wallner et al in 1997, who noted that it occurred most often between 12 to 30 months after prostate brachytherapy.[11] Since then, the PSA bounce has been described amply (Table 2)[12–22] and generally occurs within the first 30 months after treatment (Fig. 2A-C). The PSA bounce occurs in up to 62% of patients after brachytherapy and has been characterized as either a PSA rise of 0.1 ng/mL or 0.4 ng/mL or a PSA rise that exceeds >35% of nadir levels followed by a subsequent fall in the absence of intervention. Outcomes for men who experience a PSA bounce are equivalent to, if not better than, outcomes for men who do not experience a PSA bounce.[23]

In the MD Anderson Cancer Center report that prompted the current analysis, almost half of the patients with documented recurrence according to the prostogram definition actually had experienced a PSA bounce with no evidence of clinical recurrence,[6] findings that are confirmed by those of the current study. Indeed, all patients in the current study were required to have at least 30 months of follow-up to account for the PSA bounce phenomenon. With a median follow-up of 55 months at Princess Margaret Hospital, 86 months at Seattle Prostate Institute, and 60 months at University Medical Center Utrecht, data from each institution could be used to definitively establish whether a rise in PSA within the first 2 years was a benign PSA bounce or a biochemical failure. At 2 years, 54.4% of the prostogram-defined biochemical

Table 2. Studies Documenting the "Prostate-Specific Antigen Bounce" Phenomenon

Reference	No. of Patients	Clinical Stage	Hormone Therapy	External-Beam Radiotherapy	Definition of PSA Bounce[a]	Frequency, %	Time to Onset, mo	Duration, mo	Magnitude of PSA Increase (Range), ng/mL
Critz 2000[12]	779	T1-T2	No	All	0.1	35	18	6	0.4 (0.1-15.8)
Cavanagh 2000[13]	591	NA	No	Some	0.2	36	20.4	NA	1.1
Das 2002[14]	186	T1-T2	No	Some	15%	62	26.4	12	0.6 (0.5-2.5)
Merrick 2002[15]	218	T1b-T3a	No	Some	0.2	24	16.3	16	0.9
Stock 2003[16]	373	T1a-T2c	No	No	0.1	31	19.5	NA	NA
					0.4	17	19.5	NA	NA
					35%	20	20.5	NA	NA
Critz 2003[17]	1011	T1a-T2c	No	All	0.1	41	20	8	0.5 (0.1-11.8)
Crook 2007[18]	275	T1-T2	No	No	0.2	40	15.2	7	0.76 (0.21-11.79)
Mitchell 2008[19]	205	T1c-T2b	No	No	0.2	37	14.9	11.3	0.91 (0.2-5.8)
Satoh 2009[20]	388	T1-T2	No	No	0.1	51	12	NA	0.4 (0.1-6.62)
					0.4	24	18	NA	
					35%	19	18	NA	
Kanai 2009[21]	86	T1-T2	No	No	0.4	33	15	NA	0.62 (0.41-3.71)
Zwahlen 2011[22]	194	T1-T2	No	No	0.2	50	14	12	0.5 (0.2-8.3)
					0.4	34	14	13	0.8 (0.4-8.3)
					15%	11	16	18	1.9 (0.4-8.3)
					35%	9	15.5	21.5	2 (0.4-8.3)

Abbreviations: NA, not available; PSA, prostate-specific antigen.
[a] Units refer to increases of ng/mL or percentage of previous value.

failures were benign PSA bounces and not biochemical failures.

Validated nomograms have become widely used tools for clinical decision-making in prostate cancer.[3] However, the current report indicates the inadequacy of nomograms when they are not updated to reflect the changing definitions of what constitutes a treatment failure of a particular treatment modality and, as a result, become invalid. Furthermore, predictive nomograms generally reflect the outcomes of high-volume centers, which may not accurately reflect the experience of lower volume centers. According to a recent publication from Memorial Sloan-Kettering Cancer Center, 80% of clinicians who perform radical prostatectomies do fewer than 10 such operations per year; moreover, the same group estimated that, at this rate, most clinicians would not achieve an adequate level of proficiency over the course of their clinical practice.[24] Therefore, for clinicians to use published nomograms that are based on data from high-volume centers to counsel patients on their predicted outcomes may be misleading, because their patients may not be obtaining comparable treatment.

In conclusion, the widely used prostogram does not accurately predict outcomes in terms of biochemical recurrence after modern-day prostate brachytherapy. Problems with the validity of the prostogram arise mostly from its inability to distinguish benign PSA bounces from true biochemical recurrence, particularly during the first 2 to 3 years after treatment. Until the prostogram can accommodate the PSA bounce phenomenon, clinicians and patients should avoid both using the prostogram to predict probabilities of cure after prostate brachytherapy and comparing predicted outcomes with actual outcomes after external-beam radiotherapy and surgery.

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CONFLICT OF INTEREST DISCLOSURES

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