

A Nomogram Predicting 10-Year Life Expectancy in Candidates for Radical Prostatectomy or Radiotherapy for Prostate Cancer

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Submitted December 13, 2006; accepted May 1, 2007.

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

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0732-183X/07/2524-3576/\$20.00

DOI: 10.1200/JCO.2006.10.3820

ABSTRACT

Purpose

Candidates for definitive therapy for localized prostate cancer (PCa) should have life expectancy (LE) in excess of 10 years. However, LE estimation is difficult. To circumvent this problem, we developed a nomogram predicting 10-year LE for patients treated with either radical prostatectomy (RP) or external-beam radiation therapy (EBRT) and compared it with an existing tool.

Patients and Methods

Between 1989 and 2000, 9,131 men were treated with either RP (n = 5,955) or EBRT (n = 3,176), without any secondary therapy and all deaths were considered unrelated to PCa. Age and Charlson comorbidity index (CCI) predicted 10-year LE in Cox regression models. We used 200 bootstrap resamples to internally validate the nomogram.

Results

Median age was 66 years, median CCI was 1, median follow-up was 5.9 years and median actuarial survival was 13.8 years. Advanced age ($P < .001$), elevated CCI score ($P < .001$) and treatment type (EBRT v RP, $P < .001$) were independent predictors of poor 10 year LE. The nomogram predicting 10 year LE after either RP or EBRT was 84.3% accurate in split sample validation and was 2.9% ($P = .007$) more accurate than the existing tool. A cutoff of 70% or less was 84% accurate in identifying men who did not survive beyond 10 years.

Conclusion

Our nomogram can accurately identify those individuals who do not have sufficient LE to warrant definitive PCa treatment and can help optimizing therapy decision-making.

J Clin Oncol 25:3576-3581. © 2007 by American Society of Clinical Oncology

INTRODUCTION

The 10-year rule is the most frequently cited life expectancy (LE) benchmark for delivery of definitive therapy to patients with localized prostate cancer (PCa). This rule has been adopted by several professional associations and appears in their guidelines.¹⁻³ In Canada, the average LE of men age 65 years is 17.0 years versus 10.3 years for 75-year-olds versus 7.7 years for 80-year-olds versus 18.4, 11.8, and 9.0 years in the United States, respectively.^{4,5} Based on the 10-year LE, men up to 75 years qualify for definitive PCa therapy. In those men comorbidities and PCa compete for LE.^{6,7} Albertsen et al, in their series of men treated with watchful-waiting and delayed intervention, demonstrated that 63% of those with intermediate grade PCa (Gleason sum 6) and ages 65 to 69 years at diagnosis, die of noncancer causes.⁷ Therefore, rec-

ommendations favoring therapy with curative intent in older individuals may result in significant over-treatment.

Predicting LE of candidates for definitive PCa therapy, such as radical prostatectomy (RP) or definitive external-beam radiation therapy (EBRT), is difficult and literature suggests that clinicians are poor judges of LE.^{8,9} Three prognostic tools were designed by Tewari et al, Cowen et al, and Albertsen et al to assist with this task.¹⁰⁻¹² The limitation of these tools resides in their modest accuracy (69% to 73%).¹⁰⁻¹² Moreover, neither of these dissociates the contribution of PCa mortality from the effect of non-PCa mortality, when LE is predicted. We believe that cancer-related mortality risk should ideally be removed from pretherapeutic LE predictions, as the effect of PCa therapy is unknown at the time of treatment decision making. Thus, we devised a tool for prediction of 10-year LE after RP or EBRT in a

large population-based cohort ($N = 9,131$), restricted to PCa patients who did not receive any secondary therapy. We compared our model with the model of Tewari et al. We also defined several cutoffs to assist the clinician with identification of individuals with insufficient LE to warrant definitive therapy.

PATIENTS AND METHODS

Study Cohort

In Canada, health care is under independent administrative control by 11 provinces or territories. In the Province of Quebec, the Quebec Health Plan represents the exclusive insurer. Its database is used for billing purpose and allows virtually complete ascertainment of all health services and medications covered by the plan.^{13,14} These contain all treatment modalities for PCa and include RP and EBRT, as well as all types of hormone manipulation (HM). HM consisted of either medical androgen deprivation therapy (ADT) with luteinizing hormone releasing hormone agonists, steroidal or nonsteroidal antiandrogens, or bilateral orchiectomy. Moreover, the health plan relies on the ninth version of the International Classification of Diseases (ICD-9) and the respective dates of all disease codes since June 1, 1983. These allow defining the Charlson comorbidity index (CCI) scores at the time of definitive therapy.¹⁵ The CCI can predict the risk of mortality according to existing comorbidities.^{16,17} The D'Hooe adaptation of the CCI was used to define the burden of comorbid disease based on ICD-9 codes.¹⁷ Survival was defined according to patient's vital status in the health plan data file as of June 30, 2004.

The health plan database allowed us to identify all men diagnosed with PCa (ICD-9 185). We used the respective RP and EBRT billing codes to identify patients who received one or both therapy modalities. Analyses were restricted to men treated between January 1, 1989, and December 31, 2000. Each record included the type of treatment and the respective date of RP or the starting date of EBRT, the type and date of any secondary therapy, age, and CCI score before therapy. The health plan records contain no information on PCa stage, grade, preoperative prostate specific antigen (PSA), or specific cause of death.

Overall 17,570 patients were identified. To exclude the effect of PCa-specific mortality on the overall survival, only men who did not receive any secondary therapy for PCa were included in the analysis, as information on cause specific mortality was not available. Secondary therapy was defined as either EBRT after RP or RP after EBRT. The definition also included any type of HM after either RP or definitive EBRT.

We excluded records of men treated with any form of HM before or immediately after RP (0 to 6 months) or start of EBRT (0 to 12 months), as it is difficult to establish whether HM within 0 to 12 months after EBRT or within 0 to 6 months after RP is based on adjuvant or salvage criteria. Based on the same consideration, we also excluded all men treated with bilateral orchiectomy before or after EBRT or RP. This restriction resulted in 9,131 assessable patients. Of these patients, 5,955 were treated with RP and 3,176 received definitive EBRT.

Statistical Analyses

Comparison of means relied on the independent sample *t*-test. The model development phase relied on probability estimates of survival calculated with the Kaplan-Meier method. Univariable and multivariable analyses were conducted with Cox proportional hazards regressions addressing overall mortality. The multivariable Cox regression coefficients were used to develop a nomogram predicting the probability of 10-year LE after definitive therapy for individual patients based on the S-PLUS version 1 (MathSoft Inc, Seattle, WA) environment, using the Hmisc and Design libraries. This was done by calculating the linear predictor quantifying the probability of survival at the specify time point of 10 years after RP or EBRT. Due to important differences in survival according to treatment type, which could not be accounted for by age and comorbidity alone, we decided to include treatment type as a survival predictor in the nomogram. Because treatment type may relate to comorbidities, we tested the statistical significance of the interaction term between treatment type and CCI (CCI = 0, CCI = 1, CCI = 2, CCI = 3, CCI $\geq$ 4).

The nomogram-derived 10-year LE predictions were validated by subjecting the nomogram to 200 bootstrap resamples, as a means of calculating a relatively unbiased measure of its ability to discriminate among patients. The discrimination refers to the ability of the nomogram to rank patients by their risk of mortality, such that a patient with a higher predicted risk should be more likely to die. The discriminative accuracy was quantified using the Harrell's concordance index, which is similar to an area under the receiver operating characteristics curve and applicable to time to event data.¹⁸ The accuracy is expressed as a value between 50% and 100%, where 100% indicates perfect predictions and 50% is equivalent to a toss of a coin.¹⁹ Moreover, we assessed the effect of the interaction term between treatment type and CCI on the accuracy of the model. Subsequently, the relationship between the nomograms predicted probabilities of 10-year LE and the observed 10-year survival rates was graphically explored in a calibration plot using the *val.surv* function for censored data from the R statistical software (Statistics Department, University of Auckland, New Zealand).

The Tewari et al model,¹¹ which predicts 10-year LE according to race, CCI, age, biopsy Gleason, PSA, and treatment type, was used as a comparison benchmark for the newly developed nomogram. LE predictions according to the Tewari et al model were generated assuming the lowest grade (Gleason $\leq$ 6) and lowest PSA (0 to 9.9 ng/mL) because individuals with those PCa characteristics are the most likely not to require any secondary therapy and are most similar to our cohort.¹¹ Its predictive accuracy (PA) was explored in the entire cohort. The Mantel-Haenszel test was used to compare the difference between the accuracy of our nomogram and that of the Tewari et al model.

Finally, we tested the nomogram cutoffs associated with optimal negative predictive value designed to assist the physician with identification of individuals with insufficient LE. Patients who were alive but had a follow-up shorter than 10 years were excluded ($n = 4,709$) from this part of the analyses, resulting in a subcohort of 4,422 patients among which 2,710 deaths were recorded (61.3%).

All statistical tests were performed using S-PLUS Professional, version 1 and R statistical software. All tests were two sided with a significance level set at .05.

RESULTS

In the Province of Quebec, between 1989 and 2000, 17,570 patients were treated with either RP or definitive EBRT for PCa. Of these, 5,955 patients (65.2%) and 3,176 patients (34.8%) were respectively treated with RP or EBRT without any secondary therapy and were considered PCa failure free (Table 1). Median follow-up was 5.9 years (RP, 7.0 v EBRT, 3.9) and 1,712 men (18.7%) had a follow-up beyond 10 years. Median age was 66 years (RP, 64 v EBRT, 71; $P < .001$) and median CCI was 1 (RP, 1 v EBRT, 2; $P < .001$). The median actuarial survival was 13.8 years (RP, not reached v EBRT, 4.7). The overall 10-year survival probability was 63.5% (RP, 81.1% v EBRT, 30.4%; log-rank $P > .001$; Fig 1).

In univariable Cox regression analyses, continuously coded age ($P < .001$), continuously coded CCI ($P < .001$), and treatment type ($P < .001$) represented statistically significant predictors of overall mortality (Table 2). When the other variables were held constant, each increase in age of 1 year was associated with a 1.1-fold higher likelihood of overall mortality ($P < .001$). Similarly, each increase in CCI of 1 unit was associated with a 1.4-fold higher likelihood of overall mortality ($P < .001$). Delivery of EBRT, was associated with a 6.6-fold higher likelihood of overall mortality ($P < .001$) when compared with the delivery of RP.

In multivariable Cox regression analyses, after adjusting for CCI and treatment type, the effect of age on overall mortality remained the same (rate ratio = 1.1; $P < .001$). Conversely, the magnitude of the effect of CCI ($P < .001$) and treatment type ($P < .001$) decreased as evidenced by rate ratios of 1.2 and 3.8 and versus 1.4 and 6.6 in

Table 1. Characteristics of Men Who Did Not Receive Secondary Therapy for Prostate Cancer After Radical Prostatectomy or External-Beam Radiation Therapy (N = 9,131)

Variable	All Patients		Radical Prostatectomy		External-Beam Radiation Therapy	
	No.	%	No.	%	No.	%
Total	9,131	100	5,955	65.2	3,176	34.8
Age at treatment, years						
Mean		66.4		64.2		70.6
Median		66		64		71
Range		55-93		55-89		55-93
50-59	1,372	15.0	1,188	19.9	184	5.8
60-69	5,055	55.4	3,886	65.3	1,169	36.8
70-79	2,409	26.4	855	14.4	1,554	48.9
≥ 80	295	3.2	26	0.4	269	8.5
Charlson comorbidity index						
Mean		1.5		1.1		2.3
Median		1		1		2
Range		0-12		0-11		0-12
0	3,389	37.1	2,704	45.4	685	21.6
1	1,970	21.6	1,397	23.5	573	18.0
2	1,703	18.7	1,024	17.2	679	21.4
3	950	10.4	472	7.9	478	15.1
4	552	6.0	221	3.7	331	10.4
5	281	3.1	77	1.3	204	6.4
6	158	1.7	40	0.7	118	3.7
≥ 7	128	1.5	29	0.4	108	3.4
Follow-up time, years						
Median		5.9		7.0		3.9
Mean		6.3		7.4		4.3
Range		0.1-15.5		0.1-15.5		0.1-15.5
Deaths	2,875	31.5	903	15.2	1,972	62.1
Actuarial survival, years						
Median		13.8		Not reached		4.7
Mean		10.7		13.0		6.4
Overall survival probabilities						
5 year		77.0		92.0		48.8
10 year		63.5		81.1		30.4
15 year		46.3		61.9		17.9

univariable analyses, respectively. The interaction between CCI and treatment type was tested and it failed to demonstrate statistical significance ($P = .2$).

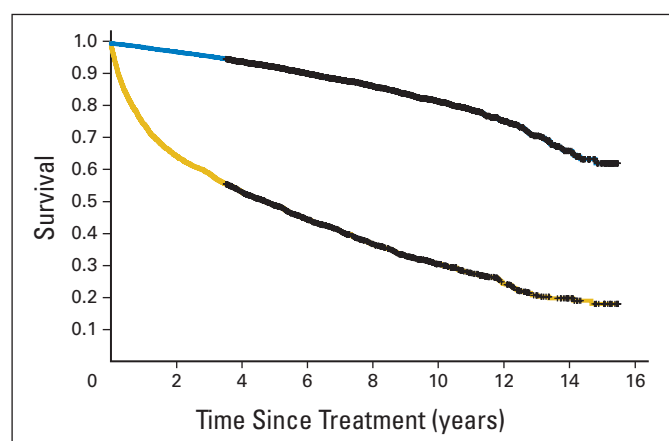


Fig 1. Overall survival in men, who did not receive secondary therapy after radical prostatectomy (RP) or external-beam radiation therapy (EBRT), stratified according to treatment type (N = 9,131). The blue line represents survival of men treated with RP. The yellow line represents survival of men treated with EBRT. Black crosses (+) represents events (deaths) and are superimposed over each line.

The multivariable Cox model was used to develop a nomogram predicting the individual probability of 10-year LE after either RP or definitive EBRT (Fig 2), which demonstrated 84.3% accuracy in the internal validation. The use of an interaction term between CCI and treatment type did not improve the PA of the model (84.4%).

The relationship between nomogram predicted probability of 10-year LE and the observed fraction surviving is shown in Figure 3 and indicates virtually perfect predictions throughout the range of predicted probabilities. The Tewari et al model demonstrated 81.4% accuracy in our cohort. The difference in PA of the Tewari et al model was statistically significantly lower ($P < .001$) than the PA of our model.

Table 3 illustrates the ability of various nomogram cutoffs to identify those with a low probability of 10-year LE after RP or definitive EBRT. Data include the percentage of patients in whom definitive therapy should not be considered based on inadequate LE prediction.

DISCUSSION

Delivery of definitive therapy to individuals whose tumor characteristics are too indolent to threaten their LE represents overtreatment, which may unnecessarily add to costs, complications, adverse effects, early and late morbidities, as well as treatment-related mortality.^{7,20}

Table 2. Univariable and Multivariable Cox Regression Analyses of the Effect of Age, CCI, and Treatment Type on Overall Mortality in Men Who Did Not Receive Secondary Therapy After RP or EBRT (N = 9,131)

Variable	Univariable			Multivariable		
	Rate ratio	95% CI	P	Rate ratio	95% CI	P
Age at treatment						
Continuously coded	1.13	1.12 to 1.14	< .001	1.07	1.06 to 1.07	< .001
CCI						
Continuously coded	1.35	1.33 to 1.38	< .001	1.16	1.13 to 1.20	< .001
Treatment type						
EBRT v RP	6.56	6.06 to 7.11	< .001	3.80	3.47 to 4.12	< .001

Abbreviations: RP, radical prostatectomy; EBRT, external-beam radiation therapy; CCI, Charlson comorbidity index.

Thus, from a societal as well as individual perspectives, individuals with suboptimal LE should not be considered for definitive therapy, but should be offered expectant management with delayed intervention.⁷

The aforementioned considerations clearly indicate the importance of LE in treatment decision making. However, accurate prediction of LE in PCa patients represents a challenge. Besides empirical predictions, clinicians can be assisted with several prognostic tools. These consist of life tables, comorbidity indices, and three prognostic models.^{4,10-12}

The life tables represent an average prediction of the remaining life years based on sex and age characteristics. The ability of the life tables to predict individual patients' LE is unknown. Moreover, life-table predictions may be further undermined based on their reliance on average LE.²¹ Population averages may not apply to patients with localized PCa, who are generally healthier.¹¹ Various comorbidity indices can also assist with LE estimation, where the CCI is the most widely used in medical literature.^{6,12,16,22}

Several investigators combined the CCI with age and PCa characteristics in an attempt to predict LE in men treated with definitive therapy.¹⁰⁻¹² Cowen et al used data from 506 patients to develop a nomogram predicting 5-, 10-, and 15-year LE in PCa patients treated with either RP, radiotherapy, or conservative management. Predictors included age, CCI, general performance, angina history, blood pressure, body mass index, tobacco use, marital status, PSA, Gleason sum, clinical stage, and treatment type. Predictive accuracy was 73%.¹⁰

Tewari et al developed a similar tool in 1,611 PCa patients. The model relied on race, CCI, age, biopsy Gleason, PSA, and treatment type, and was 69% accurate.¹¹ Finally, the model of Albertsen et al (n = 451) resides on comorbidity, age, and Gleason sum, and was 71% accurate, in an external validation.^{10,12}

The limited PA of existing tools prompted us to re-explore the possibility of developing a more accurate prognostic model. Moreover, the objective of our study was to identify men who died of nonprostate cancer-related causes within 10 years of definitive therapy. Therefore, we restricted our analysis to men who did not receive any secondary therapy after their initial PCa treatment. It is virtually impossible for a patient to die of relapsed PCa without being treated with at least HM. Therefore, it can be postulated that our cohort was without evidence of clinically relevant PCa relapse and that PCa unrelated causes exclusively contributed to the observed mortality.

Our results demonstrated that 63.5% of our cohort survived beyond 10 years. The Kaplan-Meier plot (Fig 1) demonstrates the survival disadvantage related to treatment type (RP, 81.1% v EBRT, 30.4%; log-rank $P < .001$). Advanced age, multiple comorbidities, and definitive EBRT represented important predictors of poor survival at 10 years (all P values $< .001$). Men treated with EBRT were older than their surgical counterparts ($P < .001$) and had more comorbidities ($P < .001$), which were adjusted for in the model.

The survival benefit of RP patients suggests that variables that are not defined by either age, comorbidity, or cancer characteristics affect

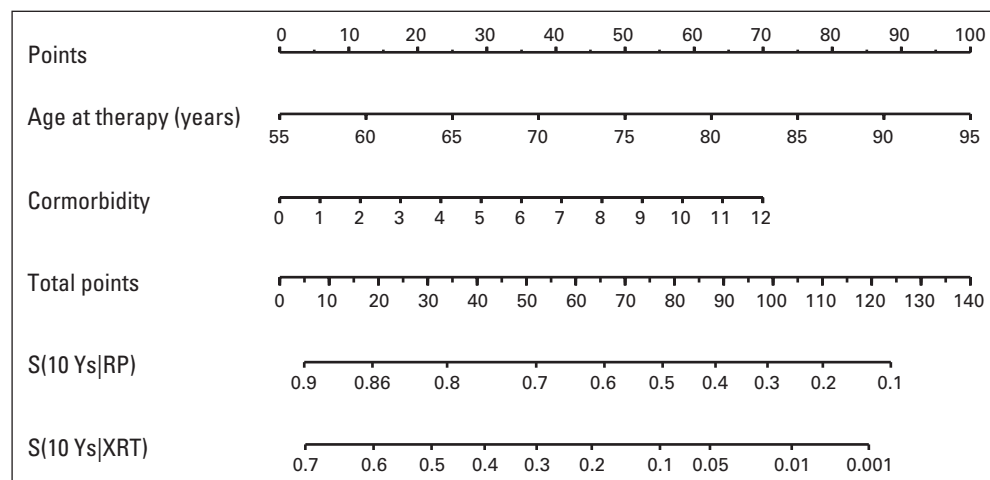


Fig 2. Nomogram predicting the probability of 10-year life expectancy (LE) after radical prostatectomy (RP) or external-beam radiation therapy (EBRT). S(10 Y) indicates probability of 10-year survival after RP. S (10 Ys|XRT) indicates the probability of 10-year survival after radiation therapy. Nomogram instructions: to obtain nomogram predicted probability of 10-year life expectancy (survival) after treatment, locate patient values at the age and comorbidity axes. Draw a vertical line to the "Point" axis to determine how many points are attributed for each variable value. Sum the points for both variables. Locate the sum on the "Total Points" line and draw a vertical line to the appropriate probability scale, based on the proposed treatment (RP or EBRT), to obtain the predicted probability of 10-year LE.

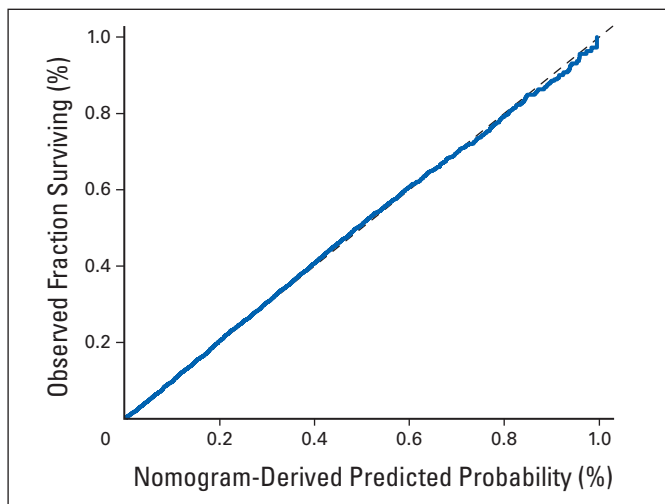


Fig 3. Calibration plot of the nomogram predicting the probability of 10-year life expectancy after radical prostatectomy or external beam radiation therapy. Nomogram predicted probabilities are compared with the observed fraction of 10-year survival. Perfect prediction would correspond to a slope of 1 (diagonal 45° broken line). Solid line indicates nomogram performance.

patient survival. This observation led to inclusion of treatment type in the final nomogram, which is consistent with other models.^{10,11} These findings are also consistent with other reports from the United States, where EBRT is delivered more frequently to older and sicker men.^{10,11,23-28} For example, in a series of 276 patients treated with either RP (*n* = 138) or EBRT (*n* = 138), Fowler et al²⁸ demonstrated that the effect of the same comorbidity score had a stronger effect on mortality in EBRT patients than in those treated with RP. A comorbidity score of 1 was associated with 77% 10-year survival after RP versus 27% in the EBRT group. The age adjusted mortality risk was 3.8 times greater (*P* = .02) in men treated with EBRT versus RP.²⁸ Our data virtually replicate those findings, as 10-year survival estimates and hazard rates for treatment type are very comparable. Based on this observation, we tested the significance of an interaction term between

treatment type and CCI. The analysis demonstrated that it was neither statistically significant nor did it improve the PA of the nomogram and therefore it was not included in the final version of the nomogram.

The nomogram predicting the probability of 10-year LE after either RP or EBRT (Fig 2) was 84.3% accurate in the internal validation. It showed higher PA than previously reported for similar tools (PA, 69% to 73%).¹⁰⁻¹² The plot demonstrating the performance of the nomogram showed virtually perfect characteristics (Fig 3). Besides better accuracy than the previous tools and excellent performance characteristics, our nomogram has several advantages, which distinguish it from other models.¹⁰⁻¹² Compared with the Cowen et al nomogram, our nomogram relies only on three predictors, instead of 11, which significantly decreases the complexity of our model.¹⁰ Relative to Cowen et al and Albertsen et al, our model also benefits of the advantage of being based entirely on patients from the PSA era.^{10,12} In addition, our model was significantly more accurate than that of Tewari et al (84.3% v 81.4%; *P* < .001) when we performed a head-to-head comparison.¹¹ The similarity of accuracy estimates between the two models demonstrates that the characteristics of PCa patients from the United States are comparable with those from Canada when LE is considered. Finally, our model was devised in a larger cohort, relative to the other tools, which makes it highly generalizable.¹⁰⁻¹² Our tool is accompanied by predicted probability cutoffs (Table 3), which can be used to interpret the nomogram predictions in clinical practice. For example, if a clinician decided not to deliver definitive therapy in individuals whose probability of 10-year LE is below 70%, the nomogram would have a negative predictive value of 84%, which corresponds to the ability to correctly identify those individuals with a LE less than 10 years. Alternative cutoffs can be chosen. Patients with a low nomogram predicted probability of 10-year LE might be offered alternative treatment modalities, such as watchful waiting with delayed intervention.¹⁻³

Our study is not devoid of limitations. Lack of cause-specific mortality represents one of the main limitations. Instead of restricting to patients without secondary therapy, we could have excluded those who died of PCa, if that information would have

Table 3. Nomogram-Derived Probability Cutoffs for 10-Year LE After Radical Prostatectomy or External-Beam Radiation Therapy in Men With 10-Year or Longer Follow-Up or Who Died During the Study Period (*n* = 4,422)

Nomogram-Derived Probability of 10-year LE (%)	Patients Below Cutoff (of total)		TN*		FN†		TP‡		Negative Predictive Value (%)
	No.	%	No.	%	No.	%	No.	%	
10	371	8.4	364	13.4	7	0.4	1,705	99.6	98.1
20	738	16.7	712	26.3	26	1.5	1,686	98.5	96.5
30	1,159	26.2	1,089	40.2	70	4.1	1,642	95.9	94.0
40	1,623	36.7	1,490	55.0	133	7.8	1,579	92.2	91.8
50	1,940	43.9	1,739	64.2	201	11.7	1,511	88.3	89.6
60	2,177	49.2	1,916	70.7	261	15.2	1,451	84.8	88.0
70	2,493	56.4	2,100	77.5	393	23.0	1,319	77.0	84.2
80	3,287	74.3	2,449	90.4	838	48.9	874	51.1	74.5
90	4,367	98.8	2,701	99.7	1,666	97.3	46	2.7	61.9

NOTE. For example a 10-year LE probability cutoff of 70% or lower implies that the nomogram would correctly identify 84.2% of all patients, who will not survive beyond 10 years after definitive therapy and 77% of patients who will survive beyond 10 years. Bold font highlights this example.

Abbreviations: LE, life expectancy; TN, true negative; FN, false negative; TP, true positive.

*Patients below cutoff who were correctly identified with an LE less than 10 years.

†Patients below cutoff who nonetheless survived beyond 10 years.

‡Patients correctly identified by the nomogram to survive beyond 10 years.

been available. Lack of clinical and pathologic characteristics of the cancers treated represents another potential weakness. However, as the confounding effect of PCa-specific mortality on overall survival was virtually eliminated, this might be only of limited importance. Moreover, we are well aware that treatment selection is not only based on LE and cancer characteristics. Quality of life considerations, patient and physician preferences, and treatment availability all add to the complexity of treatment selection. Finally, we performed only bootstrap validation of our model. Despite the validity of this method, a true external cohort might represent a more stringent test.²⁹ Nonetheless, the similarity in PA between the Tewari et al model and ours, suggests that men with prostate cancer from the United States are similar to those from Canada when 10-year LE after definitive therapy is considered.

In conclusion, our nomogram represents an accurate, user friendly, contemporary, and highly generalizable model for predicting 10-year LE in candidates for definitive PCa therapy. It is simpler and more accurate than its alternatives. The impact of predictions for large cohorts can be identified based on suggested cutoffs. Conversely, individual predictions can be used for clinical counseling.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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