Prediction of Indolent Prostate Cancer: Validation and Updating of a Prognostic Nomogram

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Purpose: Screening with serum prostate specific antigen testing leads to the detection of many prostate cancers early in their natural history. Statistical models have been proposed to predict indolent cancer. We validated and updated model predictions for a screening setting.

Materials and Methods: We selected 247 patients with clinical stage T1C or T2A from the European Randomized Study on Screening for Prostate Cancer who were treated with radical prostatectomy. We validated a nomogram that had previously been developed in a clinical setting. Predictive characteristics were serum prostate specific antigen, ultrasound prostate volume, clinical stage, prostate biopsy Gleason grade, and total length of cancer and noncancer tissue in biopsy cores. Indolent cancer was defined as pathologically organ confined cancer 0.5 cc or less in volume without poorly differentiated elements. Logistic regression was used to update the previous model and examine the contribution of other potential predictors.

Results: Overall 121 of 247 patients (49%) had indolent cancer, while the average predicted probability was around 20% ($p < 0.001$). Effects of individual variables were similar to those found before and discriminative ability was adequate (AUC 0.76). An updated model was constructed, which merely recalibrated the nomogram and did not apply additional predictors.

Conclusions: Prostate cancers identified in a screening setting have a substantially higher likelihood of being indolent than those predicted by a previously proposed nomogram. However, an updated model can support patients and clinicians when the various treatment options for prostate cancer are considered.

Key Words: prostate; prostatic neoplasms; biopsy; prognosis; models, statistical

Approximately 680,000 men are diagnosed with prostate cancer worldwide each year.[1] This number will increase with more extensive use of serum PSA testing. PSA screening leads to the early detection of cancers, of which some are so small, low grade and noninvasive that they may be assumed to pose little risk to the patient (indolent cancer).[2,3] Various factors are associated with indolent cancer, such as serum PSA, prostate volume on US and biopsy features, such as the presence and quantity of cancer cells. These characteristics have been combined in prognostic models, which have sometimes been presented as nomograms.[4–7] Further validation of these models is required. It is especially important to assess transportability to the screening setting, where over diagnosis and over treatment are of key concern.[8]

We validated a set of previously developed nomograms for indolent prostate cancer in a screening setting, where we hypothesized that the prevalence of indolent cancer would be higher than in a clinical setting.[7] We also updated the nomogram for application in counseling patients with screen detected cancer.

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METHODS

Patient Population

We considered 490 patients who were participating in the Rotterdam section of ERSPC and who underwent retropubic radical prostatectomy between 1994 and 2004.[9,10] All patients underwent systematic needle biopsies for prostate cancer diagnosis. Serum PSA was measured by the Hybritech® automated Tandem®-A assay before prostatic biopsy. Prostate volume was determined using 5 mm step-section planimetry. We selected patients as previously proposed according to clinical stage T1C or T2A disease based on the 1992 TNM system, pretreatment PSA 20 ng/ml or less, primary or secondary Gleason grade 3 at most in any biopsy, 50% or less positive cores, 20 mm or less total cancer in biopsy cores and at least 40 mm benign tissue in all cores.[7] These exclusions left 247 men for validation.

Needle Biopsy Specimens

Lateralized sextant systematic biopsies were obtained under transrectal ultrasound guidance. A single central pathological reviewer (THvdK) reviewed the biopsies while blinded to clinical data. He recorded the length of cancer in mm and assigned a primary and secondary Gleason grade to each core if cancer was found. We calculated the percent of cores with any cancer as well as the total mm with and without cancerous tissue.

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Radical Prostatectomy Specimens

Prostatectomies were totally embedded, following a strict grossing protocol.[11] The pathologist recorded the level of prostatic capsular invasion, seminal vesical invasion, surgical margin status and Gleason grade of the cancer. Indolent cancer was defined as total tumor volume less than 0.5 cc using computer assisted morphometric analysis of all separate tumor foci, confined to the prostate with no focal or established extracapsular extension and with no Gleason grade 4 or 5.

Validation

We compared patient characteristics in the setting of model development (clinical) to model validation (screening) with descriptive statistics. Effects of predictors on the prevalence of indolent cancer were tested with the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. The probability of indolent cancer was calculated for each patient with 3 logistic regression formulas underlying previously presented nomograms.[7] Models were based on analysis of a total of 409 patients from Baylor College of Medicine, Houston, Texas and University Hospital Hamburg-Eppendorf, Hamburg-Eppendorf, Germany. A base model consisted of the routinely available predictors PSA, clinical stage, and primary and secondary biopsy Gleason grade. A medium model added the percent of positive cores and ultrasound prostate volume to the base model. For a full model the percent of positive cores was replaced by the mm of noncancerous tissue and mm of cancer. All 247 ERSCP patients had complete data for the predictors considered in these models. Calibration in the large was assessed by comparing the average of observed vs predicted indolent cancers. A calibration slope was calculated with a logistic regression model with the (logit of) the predicted probability as the only covariable.[12] Ideally the slope is 1.[13,14] If predictions are too extreme, eg from over fitted models, the slope is less than 1 in new patients.[13] Discrimination was quantified by the AUC.[13] Sensitivity and specificity were calculated with sensitivity referring to important cancers undergoing radical prostatectomy and specificity referring to indolent cancers not undergoing radical prostatectomy.

Updating

For model updating we added 31 patients with T2B or T2C disease. The probability of indolent cancer in these men was 53% and 44%, which was similar to the rate in those with T1C and T2A (48% and 52%, respectively). Only 9 patients with T3 disease fulfilled the other selection criteria, including 3 with indolent cancer, and they were not considered further. We focused on the full model for updating since this model has previously shown significantly better performance than simpler models.[7] Simulation studies have shown that updating should start with a simple recalibration procedure.[14] The logistic formula for the full nomogram was updated with a new intercept and regression coefficients were multiplied by a calibration slope. The intercept and slope were estimated in a logistic regression model with the (logit of) the predicted probability as the only covariable.[14] A next step was to simplify spline functions to linear or logarithmic transformations for more robust prediction.[15]

We also considered extension of the model with other potential predictors, including patient age, family history, positive transrectal US, lesion diameter and screening round (1 or 2). For 88 patients in screening round 2 we examined the predictive value of undergoing earlier biopsy and PSA velocity in ng/ml per year. Finally, we derived a simple score chart based on the updated regression coefficients. For convenience the updated coefficients were chosen as multiples of 0.25 with rounding to lower values to prevent over fitting.[13] For the score chart coefficients were multiplied by 4 to facilitate practical application. The sum of the scores is related to the predicted probability of indolent cancer through logistic transformation. The score chart incorporates a calibration factor, such that predictions could be made in the clinical and screening settings. Statistical analyses were performed using SPSS®, version 11 and S-Plus®, version 6.

RESULTS

Of the 490 ERSCP patients undergoing prostatectomy there was indolent cancer in 121 of the 247 selected for validation (49%), which was a considerable higher prevalence than in the 243 who were not selected (32 of 243 or 13%). Characteristics in the 247 selected men were rather similar to those in the 409 considered in the clinical setting (table 1).[7] The main differences were in PSA (median 6.7 vs 4.5 ng/ml) and the prevalence of indolent cancer (20% vs 49%). The prevalence of indolent cancer was statistically significantly related to lower PSA, higher US volume, a lower fraction of positive cores, less cancerous tissue and more noncancerous tissue (table 2). No significant associations with clinical stage or biopsy Gleason grades were found. No other potential predictors were significant (table 2).

Validation of the previously developed base, medium and full nomograms showed poor calibration (table 3). The average predicted probability of indolent cancer was much lower than the observed prevalence (around 20% vs 49%, $p < 0.001$). The calibration slope was close to 1 for all 3 nomograms. The slope was 1.07 for the full nomogram, reflecting that average predictive effects in ERSPC data were slightly larger than previously found.[7] Discrimination of the nomograms was close to that published before with only slightly smaller AUC values.

For model updating we used natural log (ln) transformations for PSA and cancerous tissue length, and linear trans-

TABLE 1. *Characteristics of patients studied in clinical and ERSPC screening settings*

Characteristic	Clinical[7]	Screening
No. pts	409	247
Median age (25th–75th percentiles)	62 (57–66)	64 (61–67)
No. clinical T stage 1C (%)	298 (73)	162 (66)
No. biopsy Gleason grade 3 (%):		
Primary	351 (86)	220 (89)
Secondary	373 (91)	234 (95)
Median ng/ml PSA (25th–75th percentiles)	6.7 (4.9–9.1)	4.5 (3.4–6.3)
Median cc US prostate vol (25th–75th percentiles)	41 (31–56)	37 (30–51)
Median % pos cores (25th–75th percentiles)	27 (17–31)	29 (17–33)
Median mm tissue (25th–75th percentiles)	3.2 (1.5–6.0)	3.3 (1.4–7.0)
NonCa (25th–75th percentiles)	65 (56–78)	64 (55–72)
No. indolent Ca (%)	80 (20)	121 (49)

TABLE 2. *Prognostic factors in 247 ERSPC patients stratified by indolent or clinically important cancer*

	Pathological Ca Assessment		
	Indolent	Important	p Value
Previous nomogram predictors			
No. clinical T stage (%):			0.53
T1C	77 (48)	85 (52)	
T2A	44 (52)	41 (48)	
No. biopsy primary + secondary Gleason grade (%):			0.08
2+2	10 (77)	3 (23)	
2+3	5 (36)	9 (64)	
3+3	106 (48)	114 (52)	
Median ng/ml PSA (25th–75th percentiles)	4.2 (3.2–5.7)	4.9 (3.6–7.0)	0.004
Median cc ultrasound prostate vol (25th–75th percentiles)	40 (31–55)	35 (28–46)	0.006
Median % pos cores (25th–75th percentiles)	17 (17–33)	33 (17–33)	<0.001
Median mm tissue:			<0.001
Ca (25th–75th percentiles)	2 (1–4)	5 (3–8)	<0.001
NonCa (25th–75th percentiles)	67 (59–74)	62 (54–69)	0.002
Other potential predictors			
			0.95
Median age (25th–75th percentiles)	64 (61–67)	64 (61–67)	
No. family history (%):			0.46
Neg	107 (48)	115 (52)	
Pos	14 (56)	11 (44)	
No. transrectal US (%):			0.34
Neg	94 (47)	104 (53)	
Pos	27 (55)	22 (45)	
Median mm lesion diameter (25th–75th percentiles)	1.2 (0.9–1.5)	1.3 (1.0–1.4)	0.51
No. screening round (%):			0.30
1	74 (47)	85 (53)	
2	47 (53)	41 (47)	
No. earlier biopsy (%):*			0.50
No	35 (51)	33 (49)	
Yes	12 (60)	8 (40)	
Median ng/ml/yr PSA velocity (25th–75th percentiles)*	1.2 (0.9–1.5)	1.3 (1.0–1.4)	0.75
Totals (%)	121 (49)	126 (51)	

* Only screening round 2 data for 88 patients.

formations for prostate volume per 10 cc and noncancerous tissue length per 10 mm. We eliminated clinical stage since this variable had no predictive value. The prevalence of indolent cancer was 77 of 162 (48%), 44 of 85 (52%), 8 of 15 (53%) and 7 of 16 (44%) in men with clinical stage T1C, 2A, 2B and 2C, respectively. Multivariable logistic regression coefficients in ERSPC data were rather similar to previous coefficients, although some discrepancy in predictive effect was noted for Gleason grade (table 4). The 20 patients with Gleason 2 + 3 had a lower prevalence of indolent cancer than patients with Gleason 3 + 3. This implausible effect was not statistically significant and, hence, it was not accommodated in the updated model. The predictive effects of serum PSA, US volume and (non)cancerous tissue length in biopsies were slightly stronger.

TABLE 3. *Prediction accuracy of 3 previous nomograms for indolent prostate cancer in 247 ERSPC patients*

Performance Parameter	Accuracy (95% CI)		
	Base	Medium	Full
AUC:			
Kattan et al[7]	0.64	0.74	0.79
ERSPC	0.61 (0.54–0.68)	0.72 (0.66–0.78)	0.76 (0.70–0.82)
% Calibration in large:			
Predicted	24	22	15
Observed	49 (43–55)	49 (43–55)	49 (43–55)
Calibration slope:			
Predicted	1	1	1
Observed	0.78 (0.32–1.24)	0.87 (0.55–1.19)	1.07 (0.74–1.40)

Base, medium and full models were constructed before and included certain predictors and coding, that is base—serum PSA (spline transformation) + clinical stage (T2A vs T1C) + biopsy Gleason grade 1 (3 vs 2) and 2 (3 vs 2), medium—base + US volume (spline transformation) + % positive cores (spline transformation) and full—base + US volume (spline transformation) + mm cancerous tissue (spline transformation) + mm noncancerous tissue (linear transformation).[7]

The score chart starts with a score of zero if cancer is detected by screening (around 50% prevalence) (table 5). In a clinical setting with a lower prevalence of indolent cancer, eg 20%, the score is −6. PSA is highly predictive with lower values making indolent cancer more likely. Similarly less cancerous tissue in biopsies is important. Effects are smaller for larger US volume, Gleason grade 2 + 2 (vs 3 + 3) or more noncancerous tissue in biopsies. For example, a man with PSA 5 ng/ml, US volume 60 cc, Gleason grade 3 + 3 but only 2 mm cancerous tissue and 60 mm noncancerous tissue has a score of 7 + 4 + 0 + 7 + 2 = 20 points. In such a man the predicted probability is 69% (see figure).

Several treatment policies can be hypothesized in relation to the predicted probability of indolent cancer. If we did not perform surgery if the probability exceeded 60% (score greater than 18), the sensitivity to resect important cancers would be 85% and the specificity for no surgery in indolent cancer would be 46%. If we used a lower cutoff, such as a probability of greater than 30%, sensitivity would decrease to 35% and specificity would increase to 93% (table 6).

DISCUSSION

Prostate cancers identified in a screening setting had a substantially higher likelihood of being indolent than predicted by previously proposed nomograms, which were developed in a clinical setting. The only major difference be-

TABLE 4. *Logistic regression coefficients in 278 ERSPC patients to recalibrated coefficients from previous model from a clinical setting*[8]

Variables	Coefficient			p Value Difference	Coefficient Updated	Score
	ERSPC	Nomogram	Difference			
Ln(serum PSA)	−1.42	−1.25	−0.17	0.60	−1.25	−5 Points/ln
Prostate vol/10	0.32	0.23	0.09	0.32	0.25	1/10 cc
Gleason 3+3	0	0	0	—	0	0
Gleason 2+3	−0.33	0.15	−0.48	0.42	0.25	1
Gleason 2+2	1.48	1.07	0.41	0.58	1	4
Ln(mm Ca)	−0.94	−0.81	−0.13	0.57	−0.75	−3 Points/ln
NonCa/10 (mm)	0.25	0.18	0.07	0.43	0.25	1/10 mm

Coefficients from the nomogram were recalibrated by multiplying by a factor 1.1 and the exact formula to calculate the probability of indolent cancer is P(indolent) = 1/(1+exp(−[−4.196 + 0.25 * score])], where score = −5 * (ln(PSA)−3) in ng/ml + 0.1 * (US volume−20) in cc + 4 * Gleason22 [0 if false and 1 if true] + 1 * Gleason23 [0 if false, 1 if true] − 3 * (ln(mm cancerous tissue)−3) + 0.1 * (mm noncancerous tissue−40) (table 5 and see figure).

tween the 2 settings was in PSA, which was lower in the screening setting, as might be expected. However, PSA was incorporated in all of our prediction models and the predictive effects were similar in each setting, as were the predictive effects of US volume and cancerous/noncancerous tissue length in biopsies. Hence, the difference in the likelihood of indolent cancer remained largely unexplained. Systematic differences may have occurred in selection and diagnostic procedures in patients in the clinical vs the screening setting, which were not fully reflected in the distribution of known predictors.[16] Also, small differences in the classification of indolent cancer may have confounded the comparison. Recalibrating predictions was a simple and pragmatic solution to make the model applicable to the screening setting.

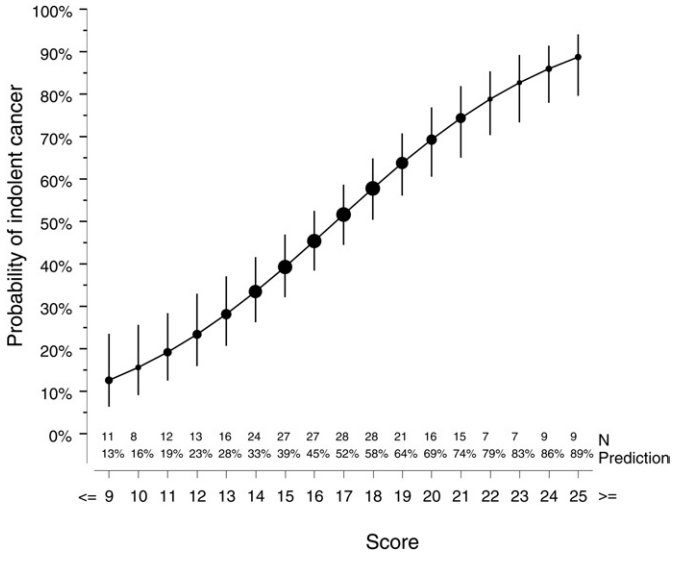
We focused on a previously published full model, which incorporates readily available characteristics such as PSA and US volume, but also requires detailed biopsy assessment of (non)cancerous tissue length.[7] The latter characteristics are of such predictive importance that their inclusion in a model is essential when predictions are made in individuals. To improve predictions in individuals new prognostic factors must be added to the full model. We found no promising results for a number of readily available characteristics, such as patient age, family history, suspicious lesions on transrectal US, lesion diameter, earlier biopsy results and PSA velocity. New markers may be useful, although careful evaluation is required with proof of incremental value over readily available predictors.[17]

Predictions in men with screen detected cancers covered a wide range with 60 of 278 (22%) having predictions below 30% (observed 10 of 60 or 17% with indolent cancer) and 84 of 278 (30%) with a prediction of greater than 60% (observed 62 of 84 or 74% with indolent cancer). Thus, in the screening setting it may be possible to predict a high probability of indolent cancer in a third of the men fulfilling the strict

TABLE 5. *Score chart for predicting indolent prostate cancer*

Variables (values)	Score
Setting specific, indolent Ca prevalence:	
50%	0
20%	−6
Serum PSA (ng/ml):	
20	0
13	2
9.0	4
6.0	6
5.0	7
4.0	8
3.3	9
2.2	11
1.0	15
Ultrasound vol (cc):	
20	0
40	2
60	4
80	6
Biopsy Gleason scores 1+2:	
3+3	0
2+3	1
2+2	4
Total mm Ca tissue in biopsy cores:	
20	0
10	2
8	3
4	5
2	7
1	9
Total mm nonCa tissue in biopsy cores:	
40	0
60	2
80	4
All score sum	—

For continuous scores (PSA, US volume and mm (non)cancerous tissue) intermediate values can be translated to scores by linear interpolation and the formula to transform the sum score to a probability of indolent cancer is P(indolent) = 1/[1+exp(−[−4.196+0.25 * score])] (see figure).



Predicted probability of indolent cancer according to sum of scores (table 6). Total of 27 patients had score of 16 points, which was median in 278 in ERSPC considered for updated model. This score corresponded to 45% probability (95% CI 38 to 52).

TABLE 6. *Sensitivity and specificity in 278 ERSPC patients with different score cutoffs for predicted probability of indolent cancer*

	No./Total No. (%)	
	Important Ca Sensitivity	Indolent Ca Specificity
Surgery in none	0/142	136/136 (100)
No surgery if p (indolent) greater than 30% (score 14 or greater)	50/142 (35)	126/136 (93)
No surgery if p (indolent) greater than 60% (score greater than 18)	120/142 (85)	62/136 (46)
Surgery in all	142/142 (100)	0/136

Sensitivity was defined as the fraction of patients with important cancer who would undergo prostatectomy with a particular cutoff for the probability of indolent cancer and specificity was defined as the fraction of patients with indolent cancer who would not undergo prostatectomy with a particular cutoff for the probability of indolent cancer.

selection criteria for this evaluation, in contrast to the clinical setting, where only few men had high predicted probabilities.[7]

Conservative management may be appropriate in patients with a high probability of indolent cancer, eg exceeding 60%. In those with a low probability, eg less than 30%, potentially curative management may possibly be advised. Note that these cutoffs for the probability of indolent cancer are speculative and further research is required to give more insight into the pros and cons of prostatectomy in men with a substantial probability of indolent cancer. Other factors may dominate the decision making process in individuals. For example, a life expectancy of less than 10 years may argue against prostatectomy. This may be the case in older men and those with comorbidities. Also, some younger men may be willing to accept the risk of metastases from an untreated tumor to avoid the risk of complications from surgery or radiotherapy. On the other hand, the model may be reassuring in some men in whom aggressive therapy is warranted. With the updated model we hope to provide objective information as a basis for this decision, rather than provide an absolute solution to the management dilemma.

Our study confirms that models can reasonably predict the likelihood that a patient has a small, well to moderately differentiated prostate cancer that is confined to the prostate. We recognize that a pathological outcome may not define the biological potential of an individual tumor. Nevertheless, it provides valuable information to a patient who is considering conservative management of prostate cancer. Importantly men who elect conservative treatment must agree to frequent examinations and repeat biopsies periodically since the risk may change with time.[18,19] Further study is required of the relation between the predicted risk of indolent cancer and outcome under a watchful waiting strategy to validate the currently arbitrary definition of indolent cancer.

Our study has some limitations. Sample size was relatively small since we made a rather limited selection of patients with screen detected cancer from the ERSPC trial. We advocate further validation of the updated model in other settings and with large numbers. For example, conclusions on the predictive value of Gleason grade were hampered by the fact that we studied only 27 patients with grade 2 at biopsy. Also, the calibration factor in our model reflects differences between patients from different settings, which are not captured by the characteristics in the current model. Further research is required to elucidate this issue. Furthermore, in this study the standard was to perform lateralized sextant biopsies. Currently many clinicians perform significantly more biopsies because this may improve cancer detection rates and Gleason scoring. It is not clear how the model will perform when more biopsies are done. Finally, the presentation of a prognostic model as a nomogram or score chart, as in this study, may be too complicated for application by clinicians, although it is simpler than a regression formula. A computerized version may be more useful, eg http://www.nomograms.org.[20]

CONCLUSIONS

Models predicting indolent prostate cancer in the clinical setting provide probabilities that are too low for cancers identified in a screening setting. However, an updated model can support patients and clinicians when the various treatment options for screen detected prostate cancer are considered.

Abbreviations and Acronyms

ERSPC = European Randomized Study on Screening for Prostate Cancer
PSA = prostate specific antigen
US = ultrasound

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EDITORIAL COMMENT

There is increasing recognition that a substantial proportion of men with screen detected prostate cancer would otherwise have not known about the disease during life in the absence of screening. In these men cancer treatment is not beneficial. These authors address the timely issue of identifying patients with newly diagnosed prostate cancer who have indolent disease for which surveillance or expectant management may be an appropriate alternative to immediate curative intervention. Recognizing that there is currently no surrogate for cancer that will remain biologically indolent during patient life and other factors, such as life expectancy and comorbidity, may be as important as the pathological characteristics of the cancer, the authors defined indolent disease based on pathological stage, tumor volume and cancer grade (organ confined tumor less than 0.5 cc with no Gleason pattern 4 or 5). When evaluating a previously described nomogram for predicting indolent cancer in the setting of a screening trial, they found that the proportion of patients with indolent cancer was higher than in the nonscreened setting in which the model was created (49% vs 20%) (reference 7 in article). It is important to emphasize that the cohort chosen for this study had lower risk features (table 1). Thus, the proportion of indolent cancer (49%) was over represented compared to all men screened. Given this selection, those with indolent cancer differed significantly from those with important cancer with respect to PSA, prostate volume, percent of positive cores with cancer, and length of cancerous and noncancerous tissue (table 2). The limitations of using currently available criteria to predict small volume, low grade cancer are similar to those in previous reports. Avoiding under treatment of men with larger volume, higher grade cancer requires treatment in a large proportion (50% or more) of those with small volume, low grade disease. In time our current methods of assessing the biological behavior of prostate cancer based on needle biopsy may be augmented or replaced by molecular profiles or panels of biomarkers that predict life threatening prostate cancer.

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