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CRITICAL REVIEW OF PROSTATE CANCER PREDICTIVE TOOLS

Shahrokh F. Shariat¹, Michael W. Kattan⁴, Andrew J. Vickers², Pierre I. Karakiewicz³, and Peter T. Scardino¹

¹ Department of Surgery, Urology Service, Memorial Sloan Kettering Cancer Center, New York, New York, USA

² Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA

³ Cancer Prognostics and Health Outcomes Unit, University of Montreal, Montreal, Quebec, Canada

⁴ Department of Quantitative Health Sciences, The Cleveland Clinic, Cleveland, Ohio, USA

Summary

Prostate cancer is a very complex disease, and the decision-making process requires the clinician to balance clinical benefits, life expectancy, comorbidities, and potential treatment related side effects. Accurate prediction of clinical outcomes may help in the difficult process of making decisions related to prostate cancer. In this review, we discuss attributes of predictive tools and systematically review those available for prostate cancer. Types of tools include probability formulas, look-up and propensity scoring tables, risk-class stratification prediction tools, classification and regression tree analysis, nomograms, and artificial neural networks. Criteria to evaluate tools include discrimination, calibration, generalizability, level of complexity, decision analysis, and ability to account for competing risks and conditional probabilities. We describe the available predictive tools and their features, focusing on nomograms. While some tools are well-calibrated, few have been externally validated or directly compared to other tools. In addition, the clinical consequences of applying predictive tools need thorough assessment. Nevertheless, predictive tools can facilitate medical decision-making by showing patients tailored predictions of their outcomes with various alternatives. Additionally, accurate tools may improve clinical trial design.

Keywords

prostate cancer; nomogram; prediction; recurrence; diagnosis; decision analysis

INTRODUCTION

In the United States, prostate cancer (PCa) is the most common solid malignancy and the second leading cause of cancer death in men [1]. PCa is a very complex disease, and the decision-making process at the basis of the management of radical treatments is challenging because it requires a fine balance among expected clinical benefit, life expectancy, comorbidities, and potential treatment-related adverse events. The prediction of clinical outcomes is therefore

Address correspondence to: Peter T. Scardino, MD, Department of Surgery, Urology Service, Weill Cornell College of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York New York 10021, Tel: 646-422-4322, ScardinoP@MSKCC.org.

Conflict of Interest Statement

MWK and PTS are co-inventors of several patents and patent applications (20070111269 Method to predict positive repeat prostate biopsy; 20050282199 Method to predict prostate cancer; 20030235816 Method to determine outcome for patients with prostatic disease). SFS is co-inventor of two patent applications (20030235816 Method to determine outcome for patients with prostatic disease; 20030054419 Method to determine prognosis after therapy for prostate cancer).

critical. Accurate estimates of stage and of the likelihood of cancer diagnosis, clinical significance, treatment success, complications, and long-term morbidity are important for patient counseling and informed decision-making. By understanding the most probable endpoint of a patient's clinical course, physicians may modify treatment and post-treatment strategies in order to balance benefits and adverse events of treatment. Prediction also allows patients to choose responsibly among the different treatment strategies proposed by the clinicians. Properly informing the patient of these likelihoods could improve his satisfaction after treatment. Lack of patient involvement in treatment decision has been identified as a major risk factor for regret of treatment choice [2,3]. Therefore, accurate estimates of risk help physicians make specific management recommendations.

Traditionally, physician judgment has formed the basis for risk estimation, patient counseling, and decision making. However, clinicians' estimates are often biased due to both subjective and objective confounders [4–7]. To obviate this problem and to obtain more accurate predictions, researchers have developed predictive tools that are based on statistical techniques [8]. Recently, predictive tools have been introduced to predict the outcome of interest for the individual patient. Predictive tools have been shown to perform better than clinical judgment when predicting probabilities of outcome [7,9,10]. That said, physician input is obviously essential in medical decision-making, both for the measurement of variables that are used in the prediction process and for the interpretation and application of prediction tool-derived outcome predictions in clinical practice.

There are a number of types of prediction tools such as Kattan-type nomograms [11,12], risk groupings [13,14–16], artificial neural networks (ANNs) [17], probability tables [18,19], classification and regression tree (CART) analyses [20,21], probability formulas, look-up and propensity scoring tables, and risk-class stratification prediction tools. In this review, we describe criteria for evaluation of predictive tools and present an inventory of available predictive tools available for PCa, which were identified in a search of MEDLINE literature from January 1966 to April 2009. For each of the tools, we describe the patient population, the outcomes predicted, and individual tool characteristics such as predictor variables, discrimination estimates, and whether the tool has been internally and/or externally validated.

EVALUATING PREDICTIVE TOOLS

Prediction tools can be compared based on several criteria: discrimination, calibration (correlation between predicted and observed risk throughout the entire range of predictions), generalizability, level of complexity, adjustment for the effect of competing risks, use of conditional probabilities, and application of decision-analysis. The most important of these considerations are discrimination and calibration.

Discrimination

A good predictive tool is able to discriminate between patients with or without the outcome of interest. Discrimination is quantified using the area under the curve (AUC) for binary outcomes (e.g., presence or absence of cancer on biopsy), the c-index for censored data (e.g. recurrence after radical prostatectomy), and the Brier score [22]. For both AUC and c-index, 0.5 represents no discriminating ability (coin flip), whereas a value of 1.0 represents perfect discrimination.

A valid determination of the prediction tool's discrimination would require the application of the prediction tool in populations other than the population used in development of the prediction tool. Thus, the discrimination should be ideally tested in an independent cohort; however, in the absence of an external cohort, prediction tools are usually subjected to internal validation. Internal validation can be done by bootstrapping (the development dataset is used to simulate prediction tool testing under novel conditions) [23–28], split-sample validation,

and/or cross-validation (such as 5-fold or 10-fold cross-validation or leave-one-out validation) [27].

Calibration

While discrimination quantifies the ability of a prediction tool to distinguish between patients, calibration quantifies the accuracy of a prediction for an individual patient. A tool is well calibrated if close to x% of patients given an x% risk have the event. Calibration plots graphically illustrate the relationship between predicted and observed rates of the outcome of interest. Ideally, a well calibrated prediction tool exhibits a 1:1 relationship between predicted and observed rates, resulting in 45 degree slope (e.g., Figure 2B). Such plots can be calculated for the data set used to create the model (in which case poor calibration is rare) or for external datasets.[24, 26–29].

Generalizability

Differences in disease and population characteristics may undermine the discrimination and calibration of predictive tools when applied to a different population. Specific criteria used in defining the sample used to develop a prediction tool may not allow the use of tools for patients with different characteristics or who have been exposed to different treatment modalities. For example, a prediction tool that is specific to screening population may perform differently when applied to a referral population [29]. Similarly, prediction tools that were developed using high-volume single center databases may not be applicable to community practice. Therefore, it is important that clinicians judge whether a specific prediction tool is indeed generalizable and applicable to the population they intend to apply it to [24,26–28]. Models that do adjust for important factors such as grade and stage are more likely to be generalizable. A model could be useful if it adjusted for the major characteristics.

A prediction tool's ability to predict a specific outcome may be affected by population characteristics that change over time. In general, more contemporary PCa patients are diagnosed with more favorable stage and grade. Therefore, prediction tools require periodic reappraisals to assess the effect of change of stage and grade on the prediction tool. One may find that predictions devised on historic cohorts are less accurate for contemporary patients. Some prediction tools, however, have shown stable performance characteristics such as discrimination and calibration [30]. External validation in contemporary cohorts is necessary to ensure continued validity.

Level of complexity

The level of complexity of a predictive tool represents an important practical consideration. One has to distinguish between complex algorithms and models with complex inputs required. Complex algorithms have fewer problems because in the future the calculations will be done by computers. However, models with complex inputs are clearly impractical in busy clinical practice. This may, however, become a moot point with the advent of “smart” medical records. On the other hand, the use of variables that are not routinely available, such as novel molecular markers, is impractical.

Adjustment for competing risks

Because of the protracted course of prostate cancer, prediction tools may need to take competing causes of mortality into consideration. Consideration of competing risks is a feature of several prediction tools for patients with bladder cancer.[31–34] Competing risk modeling is able to predict cancer control rates after accounting for the effects of competing risks. Such modeling is important if risk of non–cancer related death is high, or if predictors of death overlap with predictors of the event of interest. If risk of death is relatively low, and predictors

of death are separate from predictors of the event of interest, then adjustment for competing risks will have little effect on prediction. For PCa, it seems that there is need to better understand PCa-related risks in the context of other-cause mortality. Predictions that account for competing risks are important to clinicians, as well as to patients, especially when there is danger of over-treatment or sub-optimal treatment. Indeed, since the morbidity and mortality of PCa treatment are not trivial, clinicians must be able to better risk-stratify PCa patients to ensure that treatment is directed toward those who are most likely to benefit from it [35].

Conditional probabilities

A patient's probability of a future event changes over time; for example, a patient's risk of disease recurrence within 5 years after radical prostatectomy is higher the day after surgery than if the patient has an undetectable PSA at 48 months. In PCa, because patients' prognosis is expected to improve with increasing disease-free interval, absence of adjustment for this variable results in an excessively somber estimate of cancer control over time. The updated versions of the pre- and post-operative Kattan nomograms for prediction of biochemical recurrence provide the opportunity to adjust for the effect of disease-free interval from surgery [36,37]. As expected, the predicted risk of disease recurrence decreases with increasing disease-free interval.

Head-to-head comparison

When judging a new tool, one should compare it with established prediction tools, in order to determine whether the new prediction tool offers advantages over the available alternatives [27,28,38–44]. The most direct and unbiased criteria for comparison are the objective attributes of discrimination and calibration. Subsequently, complexity, generalizability, and other attributes may also be compared. This sort of head-to-head comparison is a better approach than judging the concordance index or AUC in isolation or against a possibly arbitrary threshold.

In a head-to-head comparison, each prediction tool being compared is applied to a common external dataset. The prediction tools are applied to each individual observation to derive the probability of the outcome of interest. The predictions are then compared against observed rates of the outcome of interest, and discrimination is calculated using the receiver operating characteristics curve. A common mistake consists of refitting a prediction tool on the same dataset on which it was constructed and describing this as external validation.

Decision-analysis

While discrimination and calibration are important, methods that incorporate clinical consequences are crucial to the evaluation of prediction tools. This type of analysis allows insight into the consequences of using a test, prediction tool, or marker in the clinic. Several methods are available. Decision curve analysis is a method that combines simplicity with efficient computations [45–48]. In brief, the method is based on the principle that the relative harms of false positives (e.g. unnecessary biopsy) and false negatives (e.g. missed cancer) can be expressed in terms of a probability threshold. For example, if a man would opt for biopsy if he was told that his risk of PCa was 20% or more, but not if his risk was less than 20%, it can be shown that he considers that harms associated with a delayed diagnosis of cancer to be four times greater than the harms associated with an unnecessary biopsy (i.e. the ratio of harms is the odds at the probability threshold). This threshold probability can therefore be used both to determine whether an individual patient's test result should be defined as positive or negative and to weight the clinical consequences of true and false. An example of a decision-curve is shown in Figure 1. The decision analytic evaluation should be performed during later stages of research and before clinical implementation of the tool.

“KATTAN-TYPE” NOMOGRAMS

Various distinct statistical methodologies have broadly been described as “nomograms.” Although widely used as a synonym for “prediction model”, the strict definition of a nomogram is a graphical calculating device that can be based on any type of function [12,23]. The nomogram usually incorporates at least two variables, which can be either continuous or categorical. The effect of the variables on the outcome of interest is represented by axes, and risk points are attributed according to the prognostic significance of the variable of interest. For example, in the nomogram in Figure 2 [37], each PSA value is assigned a unique point value that represents its prognostic significance. The ‘Total Points’ axis is used to estimate the combined effect of all predictors on the probability of biochemical recurrence. One advantage of this format is that it allows the input of continuously coded variables as well as categorically coded variables, without limit on the number of variables. This format distinguishes nomograms from look-up tables or decision trees, where continuously coded variables cannot be processed and where data availability limits the degree of stratification because of the need to avoid empty cells or dead-end branches.[49]

Nomograms are designed to extract the maximum amount of useful information from the data. For example, the primary and secondary Gleason grades are used as independent variables, rather than the Gleason sum alone. This additional information is useful because several combinations of primary/secondary Gleason grades can result in the same Gleason sum (e.g., 3+4=7 vs 4+3=7) [50], despite a different impact on prognosis.

The available PCa nomograms have been adapted for use on personal digital assistants and personal computers to facilitate their integration into daily clinical practice and research. Many of the nomograms can be found either on the Memorial-Sloan-Kettering Cancer Center (www.nomograms.org) or the University of Montreal (www.nomogram.org) websites.

CURRENTLY AVAILABLE PREDICTION TOOLS

The above discussion is meant to provide guidelines for analyzing and using predictive tools. Next, we provide an overview of predictive tools available for PCa. We describe predictor variables, the outcome of interest, the number of patients utilized to develop the tools, tool-specific features, predictive discrimination estimates, and whether internal and/or external validation has been performed. We focus on nomograms because we believe that they represent one of the most accurate tools to date.

Prediction of PCa on initial and repeat biopsy (Tables 1 and 2)

Table 1 shows tools for prediction of PCa on initial biopsy. Eastham *et al.* developed the first such tools, yielding a c-index of 0.75 [51]. Despite good discrimination, this tool suffers from limited generalizability. The tool was limited to men with suspicious digital rectal examination and serum PSA <4.0 ng/ml. In addition, the tool predicts only the results of sextant biopsies, further limiting its applicability. Chun *et al.* developed and validated tools in a population subjected to extended biopsy sampling [52]. External validation in three cohorts totaling 2900 men demonstrated 73 to 76% discrimination. Nam *et al.* developed a prediction tool that predicts an individual’s risk for PCa in a cohort of 3,108 men who underwent a prostate biopsy for the first time.[53] The dataset included a subset of 408 volunteers with normal PSA levels. The tool comprises factors that can be easily determined at the time of screening such as age, ethnicity, family history of PCa, the presence of urinary symptoms, PSA, percent free PSA, and digital rectal examination. The prediction tool’s discrimination was 74% and 77% for high-grade cancer (Gleason score ≥ 7). This was significantly greater than the AUC that considered using the conventional screening method of PSA and DRE only (62% for any cancer and 69% for high-grade cancer).

The PCPT investigators developed a risk calculator from a large randomized trial with an AUC of 0.70 for the ROC curve in the original cohort and 0.65 in the independent validation cohort. [54,55] This study is a potentially helpful additions to the growing number of prostate cancer nomograms

Table 2 shows tools for prediction of PCa on repeat biopsy, saturation and mixed indication (initial and repeat biopsy). A tool described by Lopez-Corona *et al.* was developed and internally validated (70% discrimination) in 343 men [56] and externally validated (71% discrimination) in 230 men [57]. Chun et al. developed the most contemporary repeat biopsy tool (n=1162) based on 10 or more biopsy cores [58]. In three external validation cohorts (n=582, n=961, and n=195) the nomogram yielded 73–76% discrimination.

Prediction of pathologic stage (Table 3)

Several multivariable statistical prediction tools have been proposed to estimate pathologic stage at radical prostatectomy (RP) with the intent of facilitating treatment planning (Table 3). Of these, the “Partin tables” represent the most widely used tool. These look-up tables predict pathologic stage at RP [18]. After their introduction in 1993, the Partin tables were validated in 1997 and updated in 2001 and 2007 [19,59–61]. Although the Partin tables represented a milestone in pretreatment PCa staging, they have limitations. For example, the probability of extracapsular extension (ECE) cannot be predicted in a side-specific fashion. To circumvent this limitation, Graefen et al. devised a regression tree capable of predicting ECE in a side-specific manner [21]. This prediction tool allows the identification of candidates for non-nerve sparing RP *versus* unilateral *versus* bilateral nerve-sparing RP. External validation of this prediction tool yielded 70% discrimination [60]

Ohori et al. developed a tool (n=763) to predict side-specific ECE (range of c-index: 79–81%) [62]. Validation of another side-specific prediction tool in 1118 European patients yielded 84% discrimination [63]. Compared to the Partin tables, the tool approach is more accurate and provides side-specific predictions. Moreover, the tools predict ECE independently of seminal vesicle invasion (SVI) and lymph node invasion (LNI) [18,19,61].

Koh et al. [64] and Gallina et al [65] used data from 763 patients to devise tools to predict the probability of SVI (range of c-index: 78–88%). Cagiannos et al. developed an LNI prediction tool (n=5,510) yielding 76% discrimination, compared to 74% for the Partin tables tested in the same cohort [66]. Briganti et al. developed an LNI prediction tool from 602 patients who underwent extended pelvic lymphadenectomy (76% discrimination) [67]. In addition, the same investigators developed another tool (n=565) that allows identification of patients who are at a negligible risk of LNI outside the obturator fossa (80% discrimination) and therefore may not require extended pelvic lymphadenectomy [68]. The combination of these tools allows accurate identification of the need for and extent of pelvic lymphadenectomy.

While prediction of adverse pathologic features is important for management of PCa patients, a proportion of patients harbor clinically insignificant or indolent PCa, which cannot be predicted with these tools [69]. To address this void, Kattan et al. developed three prediction tools (range of c-index: 64–79%) that predict the probability of indolent PCa [70] based on the definition of Epstein *et al.* (i.e., organ-confined cancer, 0.5 cm³ or less in volume, and no poorly differentiated elements) [71]. Steyerberg *et al.* externally validated these tools in a screening cohort (range of c-index: 61–76%) [29]. These models can reasonably predict the likelihood that a patient has a small, well to moderately differentiated PCa that is confined to the prostate. While pathologic outcome may not define the biological potential of an individual tumor, it provides valuable information to a patient who is considering conservative management of PCa.

These tools allow prediction of clinically insignificant PCa with reasonable discrimination, which may help in deciding between definitive therapy and active surveillance. 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.

Prediction of biochemical recurrence after RP (Table 4)

Before RP—Kattan *et al.* developed the first pre-treatment prediction tool (n=983), which predicts the 5-year biochemical recurrence for patients treated with RP [12]. External validation yielded accuracies of ~75% (range: 65%–83%) [72–74]. However, the 5-year endpoint is insufficient to predict the likelihood of cure after RP, as patients are still at risk of disease recurrence beyond 5 years [75–77]. Therefore, Stephenson *et al.* recently updated the pre-operative prediction tool by predicting the 10-year probability of biochemical recurrence after RP (Figure 2A; 77% discrimination) [37]. The prediction tool exhibited good calibration across the spectrum of predictions in internal validation but exhibited some optimism in external validation (Figure 2B). An added feature of the tool is the ability to estimate the probability of recurrence at any point in time from 1 to 10 years after RP, accounting for disease-free interval.

After RP—Kattan *et al.* also developed a post-operative tool for prediction of 5-year biochemical recurrence using data from 996 men treated with RP for clinically localized PCa by a single surgeon (73% discrimination) [11]. External validation yielded accuracies of 80% (range: 77%–82%) in an international cohort [78] and 83% in an African-American cohort [74]. Stephenson *et al.* updated the post-operative tool by including contemporary patients and extending predictions up to 10 years after RP while accounting for disease-free interval (Figure 3) [36]. External validation yielded a discrimination of 78% to 81% [36]. Suardi *et al.* developed the furthest-reaching prediction tool, which provides the probability of biochemical recurrence up to twenty years after RP. Their prediction tool also accounts for disease-free interval. The prediction tool's discrimination (77–83%) was confirmed in two external validation cohorts [79].

Prediction of biochemical recurrence after external beam radiotherapy or brachytherapy (Table 5)

An important aspect of pre-treatment counseling is pre-treatment estimates of the outcomes if treated with three-dimensional conformal external beam radiotherapy or brachytherapy. Table 5 shows prediction tools that predict biochemical recurrence after radiation therapy, all of them using the original American Society for Therapeutic Radiology and Oncology (ASTRO) definition of biochemical recurrence as 3 consecutive increases in PSA [80]. Kattan *et al.* developed a pre-treatment prediction tool to predict the 5-year biochemical recurrence-free probability after three-dimensional conformal external beam radiotherapy (n=1042; Figure 4) [81]. External validation within a cohort of 912 men yielded a discrimination of 76% [82,83].

The same authors developed a prediction tool that predicts 5-year biochemical recurrence-free survival after ¹²⁵I brachytherapy without adjuvant hormonal therapy (n=920, Figure 5) [84]. Two separate external validations resulted in discriminations of 61% (n=1827) and 64% (n=765). Minor differences in the population characteristics account for the different discrimination in the different validation populations.

Prediction of metastatic progression (Table 6)

To address metastatic progression after definitive therapy, Kattan *et al.* developed a prediction tool quantifying the probability of metastatic progression within five years following external beam radiotherapy (n=1,677) [85]. The prediction can be made immediately after definitive therapy. Its external validation demonstrated a discrimination of 81% (n=1,626).

Dotan *et al.* developed a tool to predict the probability of metastatic progression, defined as a positive bone scan, in 239 men with a rising PSA after RP [86]. The tool relies on detailed serum PSA characteristics including kinetics and therefore requires multiple post-recurrence PSA values. The prediction tool discrimination is 93%.

Slovin *et al.* devised a similar tool predicting the time to radiographically detectable metastases in patients with biochemical recurrence (n=148) after either RP or external beam radiotherapy. Similar to the prediction tool from Dotan *et al.*, the tool from Slovin *et al.* requires the consideration of PSA kinetics in the form of PSA doubling time and is limited to patients whose doubling time is less than 12 months [87]. The predictive discrimination of this prediction tool was 69%, but it was neither internally nor externally validated.

Armstrong *et al.* developed a tool using baseline clinical variables to predict death among men with metastatic hormone-refractory prostate cancer (n=1,006) using data from the TAX327 randomized clinical trial (three week or weekly docetaxel or mitoxantrone, each with prednisone).[88] Ten independent prognostic factors other than treatment group were included: presence of liver metastases, number of metastatic sites, clinically significant pain, Karnofsky performance status, type of progression (measurable disease progression and bone scan progression), pretreatment PSA doubling time, PSA, tumor grade, alkaline phosphatase, and hemoglobin. The predictive discrimination of this prediction tool was 69%. External prospective validation may support the wider use of this prognostic baseline model for men with HRPC treated with chemotherapy.

Prediction of survival (Table 6)

Four tools have been devised for prediction of survival in PCa patients. One predicts cause-specific survival in PCa patients exposed to hormonal therapy, regardless of the time of hormonal therapy initiation. The remaining three tools predict the probability of all-cause survival in patients with androgen-insensitive PCa (AIPC).

Porter *et al.* developed a tool for prediction of cause-specific survival in patients exposed to hormonal therapy after RP failure (n=114) [89]. The internally validated discrimination of the tool was only 66%. Among the three prediction tools for AIPC patients, those of Smaletz *et al.* [90] and of Halabi *et al.* [91] were developed and externally validated in heavily pretreated patients, who had been exposed to one to several experimental agents. In external validation, the accuracy of the prediction tool of Smaletz *et al.* was 67% and that of Halabi *et al.* was 67% and 68%.

Svatek *et al.* devised a contemporary prediction tool using a population with a median survival of 52 months who had not received experimental therapies. This prediction tool relies predominantly on PSA doubling time and PSA level at hormone therapy initiation. Internal validation of this prediction tool yielded a discrimination of 81%. The contemporaneity and homogeneity of the patient population make this prediction tool very attractive when survival needs to be assessed in patients with AIPC.

Prediction of life expectancy (Table 7)

Life expectancy is a crucial consideration in treatment decisions, especially in patients who are candidates for definitive therapy. Ten years is generally accepted as the minimal life expectancy pre-requisite for curative local treatment in men with PCa. Unfortunately, life tables are not reliable for prediction of life expectancy in definitive therapy candidates, demonstrating only 60% discrimination [92]. Moreover, clinicians are also poor raters of life expectancy, with 19 clinicians yielding only 69% discrimination. To circumvent this problem, Tewari et al. (n=3159) [93], Cowen *et al.* (n=506) [94], and Albertsen et al. (n=451) [95,96] developed prediction tools predicting life expectancy in men with PCa. The discrimination of these prediction tools ranged from 69% to 73%. Unfortunately none of the three prediction tools is capable of discerning between PCa-specific and all-cause mortality. To address these considerations, Walz et al. devised a tool for prediction of life expectancy in excess of 10 years in candidates for RP and external beam radiotherapy (n=9131) [97]. The prediction tool focused on patients without evidence of cancer relapse after definitive therapy. The predictors consist only of age and co-morbidities. Internal validation of this tool yielded 84% discrimination vs. 81% for the prediction tool of Tewari et al. Based on discrimination, simplicity, and generalizability, the prediction tool of Walz et al. appears to provide the best estimates of life expectancy in excess of 10 years.

Prediction tools of the future: inclusion of novel biomarkers and imaging tools (Table 8)

The discrimination of current predictive tools is imperfect. To date, discrimination has not been significantly improved by the addition of other potentially informative clinical and pathologic features [98,99]. Discrimination may, however, potentially be improved by incorporation of novel biomarkers and/or imaging data that are associated with the biologic behavior of PCa.

Over the past two decades, the molecular dissection of cancer has increased our understanding of the pathways that are altered in neoplastic cells. Protein expression profiling of PCa offers an alternative means to distinguish aggressive tumor biology and may improve the accuracy of outcome prediction. In addition, such markers may serve as prognosticators and/or therapeutic targets that facilitate the emergence of new therapeutic approaches.

However, despite numerous reports of promising new biomarkers in the urological literature, to date only a few studies have demonstrated an important improvement in predictive discrimination when biomarkers were added to established predictors in prediction tools (example: Figure 6) [43,97,100–105].

Kattan *et al.* [100] developed and internally validated a prognostic prediction tool that incorporates pre-operative plasma levels of transforming growth factor- β 1 and interleukin-6 soluble receptor in the standard pre-operative Kattan nomogram (which uses pre-operative PSA, biopsy Gleason grade, and clinical stage to predict the probability of biochemical recurrence-free survival at 5 years after RP) [12]. Addition of these biomarkers improved the predictive accuracy by a statistically and prognostically substantial margin relative to clinical variables alone (increase in accuracy from 75% to 83%). This prognostic tool was externally validated in an independent cohort comprising 423 consecutive men who underwent radical prostatectomy [104]. The validation prediction tool provided a discrimination of 87.9% versus 71.1% for the tool including clinical variables only (16.8% difference; $P < .001$). Moreover, the prediction tool was better calibrated than the tool including clinical variables only. These prediction tools further refine our ability to identify patients at a high risk of biochemical recurrence after radical prostatectomy.

Non-invasive diagnostic imaging, especially magnetic resonance imaging (MRI) and MR spectroscopic imaging (MRSI), has improved in recent years and is gaining widespread

acceptance for aiding PCa diagnosis, tumor localization, staging, assessment of tumor aggressiveness, and treatment planning. Investigators have used nomograms and neural network prediction tooling to predict organ-confined PCa [106], clinically significant disease [107], and biochemical recurrence after RP [108].

FUTURE GOALS

The paucity of randomized trials in PCa makes diagnostic and treatment decisions complex. Prediction tools can provide predictions that are evidence-based and at the same time individualized. Such predictions have been repeatedly shown to be more accurate than those of clinicians, regardless of their level of expertise [7,10]. Prediction tools such as nomograms have been embraced by the urologic community. The nomogram format has also been adopted in several other disciplines of oncology, including breast, colon, bladder, gastric, and lung cancers.

PCa patients need to be involved in decisions regarding management of their disease. They should know what their options are and what the consequences can be. At the core of any patient involvement would be accurate prediction of consequences and, essentially, a spreadsheet of these predictions tailored to the individual. This spreadsheet would help make consent for any medical decision truly informed. Providing this information could reduce the likelihood of regret of treatment choice, particularly when complications arise.

Continuous multivariable prediction tools such as nomograms are a highly appealing means of calculating accurate predictions with or without the use of a computer. Nomograms currently represent one of the most accurate and discriminating tools for predicting outcomes in patients with PCa [25,39–41,109–111]. When faced with the difficult decision of choosing among the treatment options for each clinical stage of PCa, patients benefit from the accurate estimates of outcomes provided by predictive tools. Equipped with these predictions, patients are more likely to be confident in their treatment decisions and less likely to experience regret in the future. However, we emphasize that the predictions must be interpreted as such; they do not make treatment recommendations or act as a surrogate for physician-patient interactions, nor do they provide definitive information on symptomatic disease progression or complications associated with treatments.

The fundamental issue of predictive tools such as nomograms pertains to their utility. Indeed, very limited data exist with respect to the impact of nomograms on medical decision-making. Although studies have shown that decision aids improve patient knowledge and affect medical decision-making behavior [112], the role of tools has yet to be studied sufficiently. There are no prospective randomized studies that clearly demonstrate that the use of prediction tools improve patient care or reduce patient anxiety, decisional conflict, or regret. A clinical trial would be very valuable for establishing the effects of prediction tools; however, whereas informing patients with predictions regarding the impact of a medical procedure seems ethical, withholding accurate outcome predictions from patients in a control group in a randomized trial does not. Such a trial would likely be associated with significant power problems, on the grounds that a nomogram would be worth using even for a small improvement in outcome. Presently, patients are using very limited quantitative information when making their decisions, and direct outcome predictions are the simplest factors for them to consider. Nevertheless, prospective evaluation of prediction tools and decision analytic methods would be beneficial.

Besides being required for improved medical decision-making, accurate risk estimates are also required for evaluation of novel markers and for design of clinical trials, for example to enable the selection of homogeneous groups of patients as study participants. Prediction tools have the potential of improving the ability of Phase II trials to discriminate between ineffective and potentially effective therapies. Prediction tools may help enroll populations that are

homogeneous with respect to risk. In addition, they would allow comparison with other studies and historical controls based on risk. For Phase III trials, prediction tools can help to ensure that eligible patients have sufficiently high levels of risk, thereby increasing event rates and reducing sample size requirements. Risk prediction tools define high-risk patients more accurately than do risk-grouping strategies [39,109]. Use of risk predictions for individual patients, therefore, decreases the proportion of low-risk patients enrolled, avoiding unethical inclusion, as well as increasing statistical power. Finally, future designs of Phase III trials should include prediction tools to increase the clinical utility of their findings. We therefore recommend the wider adoption of risk prediction tools and decision analysis in the design, analysis, and implementation of clinical trials.

Areas of future research include the integration of genomic/molecular markers and development of prediction tools that predict additional clinically significant endpoints such as clinical recurrence, cause-specific death, long-term survival, and outcomes related to morbidity and quality of life. Models that use updated post-treatment information based on biomarkers such as PSA will and do play a very important role in decisions about new treatment when recurrence is suspected.

Better modeling may allow for adjustment of the trend of decreased accuracy (discrimination ~ 60–70%) for “longer” predicted endpoints such as metastasis and survival compared to those for diagnosis, stage of PCA or disease recurrence (discrimination usually better than 70%). Moreover, with the advent of novel therapies such as laparoscopic/robotic prostatectomy, high-intensity focused ultrasound, and focal ablative therapy, tools specific to these procedures are needed.

CONCLUSIONS

Patients with PCa are heterogeneous with respect to disease aggressiveness, age, comorbidities, and personal preferences. Therefore, to obtain optimal cancer control with minimal side effects, treatment should be tailored to each individual patient and the characteristics of his tumor. In order to make an informed decision, many patients want to know their likely outcomes, and clinicians need to provide accurate estimates of these outcomes. Despite limitations, predictive tools can provide individualized, evidence-based estimates for a number of PCa endpoints, thereby helping in the complex decision-making process. Moreover, predictive tools provide an objective justification for clinical decisions, which is increasingly demanded by patients, administrators, peers, and third-party payers.

EXECUTIVE SUMMARY

- Predictive prediction tools have been repeatedly shown to be more accurate at predicting risk than are clinicians, regardless of their level of expertise.
- For evaluating and comparing predictive tools, discrimination and calibration are the most important criteria.
- Other considerations include the tools’ generalizability and complexity and it accounts for competing risks and/or conditional probabilities.
- Head-to-head comparisons are necessary to identify the most accurate tool. Towards this, the different tools’ discrimination and calibration is assessed in a common dataset that is not the same set used in development of any of the tools.
- The clinical consequences of use of prediction tools can be evaluated by decision-analysis.

Nomograms

- Nomograms are graphical calculating devices that can incorporate continuous as well as categorical variables
- A strength of nomograms is the ability to prediction tool non-linear relationships between variables and outcome, with no limit on the number of variables that can be incorporated.

Currently Available Prediction Tools

- Predictive tools are available to predict many endpoints in prostate cancer, including presence of cancer on biopsy, various aspects of pathologic stage, biochemical recurrence after treatment, progression to metastases, and survival.
- Although some of these tools exhibit good discrimination and calibration, many have not been externally validated, and few have been directly compared to other tools that predict the same endpoint.
- Incorporation of novel biomarkers or imaging results can increase the accuracy over that provided by clinical and pathologic characteristics alone.

Future Goals

- The clinical utility of predictive tools should be evaluated in prospective clinical trials.
- Prediction tools offer a way to get patients more involved in decision-making, allowing them to give truly informed consent and, perhaps, reducing the likelihood of later regret.
- Prediction tools also have potential for improving phase II clinical trials, by allowing the selection of uniform study cohorts and by providing a criterion for comparison between different trials.
- Prediction tools are still needed for a number of endpoints, including clinical recurrence, cause-specific death, long-term survival, outcomes related to morbidity and quality of life, and outcomes after novel therapies.

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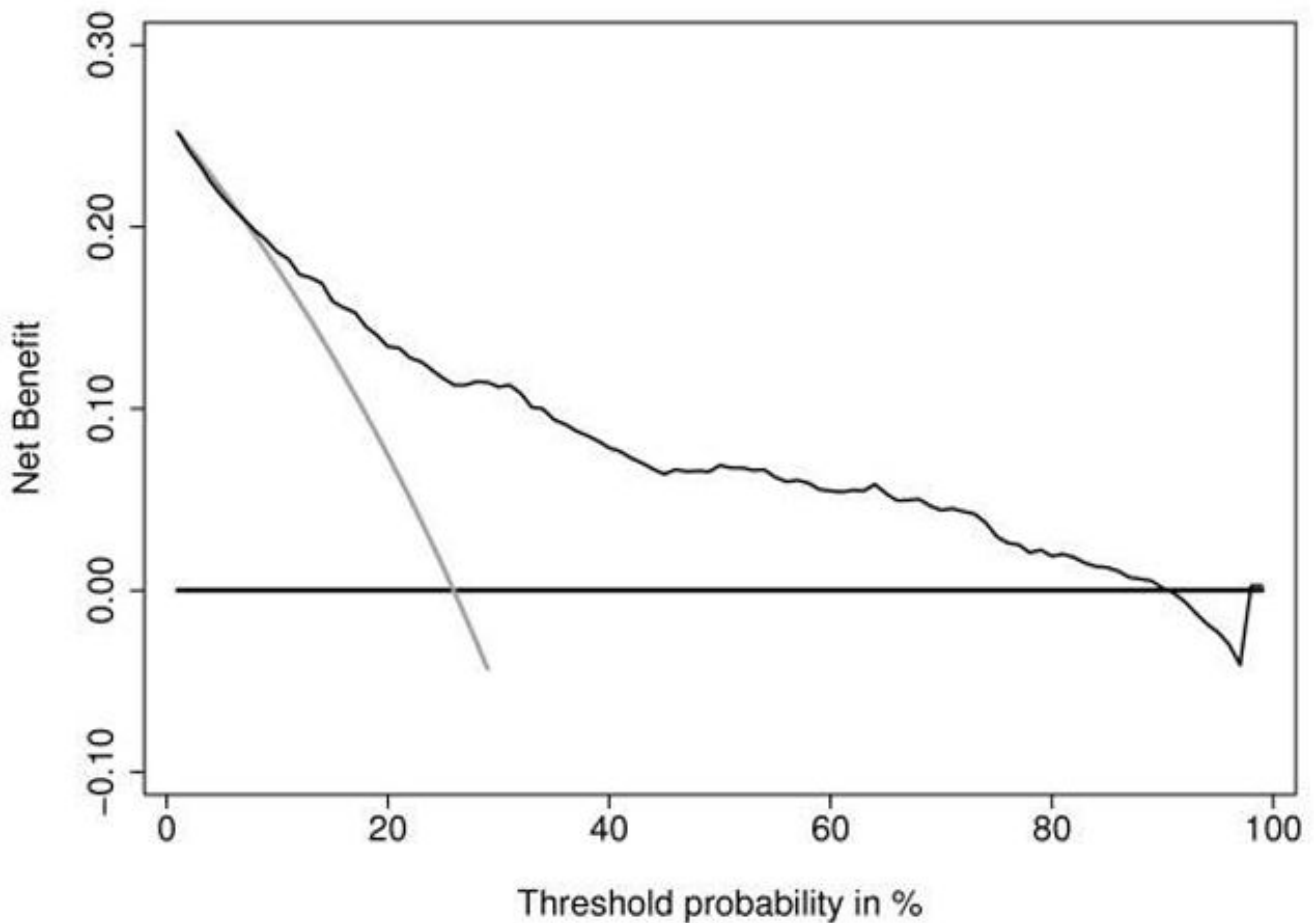


Fig 1.

Decision curve for a statistical prediction tool predicting the outcome of prostate biopsy. The thin grey line is the net benefit of biopsying all men; the thin black line is the net benefit of biopsying men on the basis of the statistical prediction tool; the thick black line is the net benefit of biopsying no man. This curve was derived from 740 men undergoing biopsy based on an elevated total PSA. The men had never been previously screened for prostate cancer. Their free PSA was measured and a digital rectal exam was performed. Approximately one-quarter (192) of the men were diagnosed with cancer. Interpretation of the decision curve depends on comparing the net benefit of the test, prediction tool, or marker with that of a strategy of “treat all” (the thin grey line) and “treat none” (parallel to the x axis at net benefit of zero). The strategy with the highest net benefit at a particular threshold probability (pt) is optimal, irrespective of the size of the difference. Determining which men should be biopsied using the statistical prediction tool was superior to biopsying all men with elevated PSA once the threshold probability reached about 10%, and was superior to the strategy of biopsying no man up to a threshold probability of about 90%. To interpret this result, one needs to consider the sort of probability for prostate cancer that men would need before they would decide to have a biopsy. A very risk-averse man might opt for biopsy even if he had only a 10% risk of cancer. However, it seems unlikely that many men would demand, say, a 50% risk of cancer before

they had a biopsy; this threshold would imply that an unnecessary biopsy is just as bad as a missed cancer. Reprinted with permission from Vickers et al. [46]

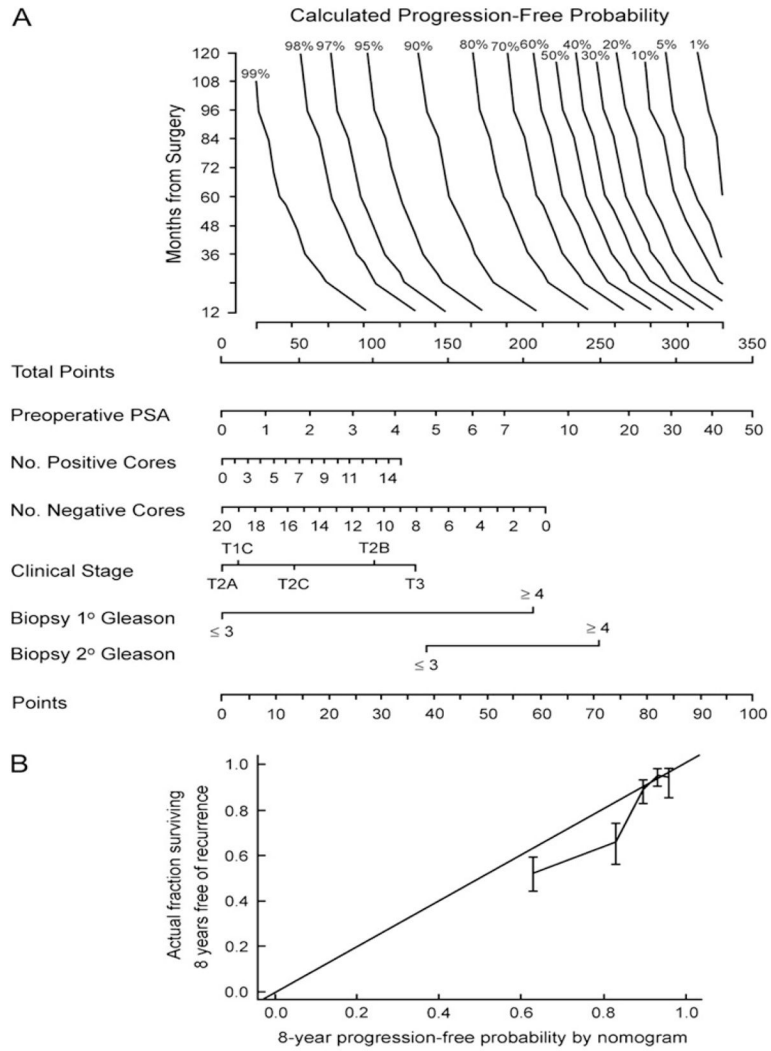


Fig 2. **A)** Pre-operative nomogram estimating the 1- to 10-year biochemical recurrence-free probability after radical prostatectomy alone. **B)** Calibration plot of the nomogram in external validation. The 45° line represents an ideal prediction tool, in which estimates of recurrence are perfectly calibrated with outcome. Vertical bars are 95% confidence intervals for quintiles in the validation set. Reprinted with permission from Stephenson *et al* [37].

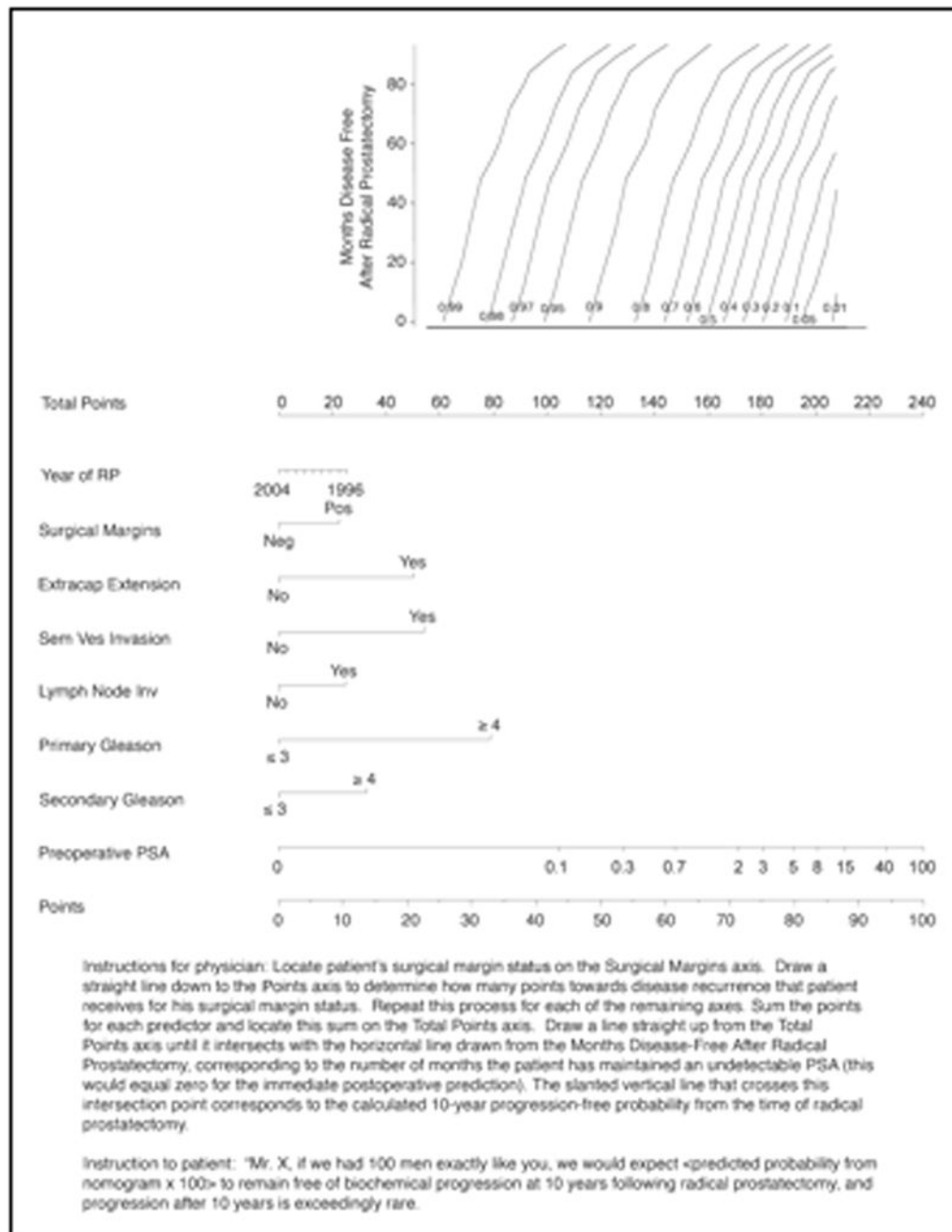


Fig 3. Post-operative nomogram predicting 10-year biochemical recurrence-free probability after radical prostatectomy. Reprinted with permission from Stephenson *et al* [36].

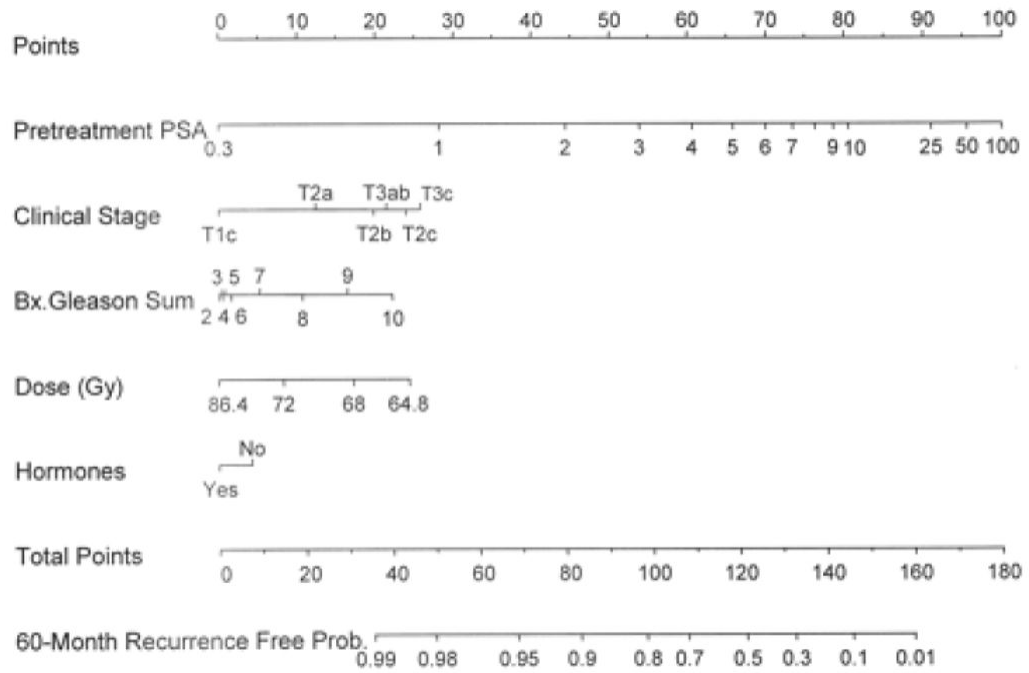


Fig 4. Pre-treatment nomogram for predicting 5-year biochemical recurrence-free probability after three-dimensional conformal radiation therapy (3D-CRT). Reprinted with permission from Kattan *et al* [81]. XRT= external beam radiation therapy.

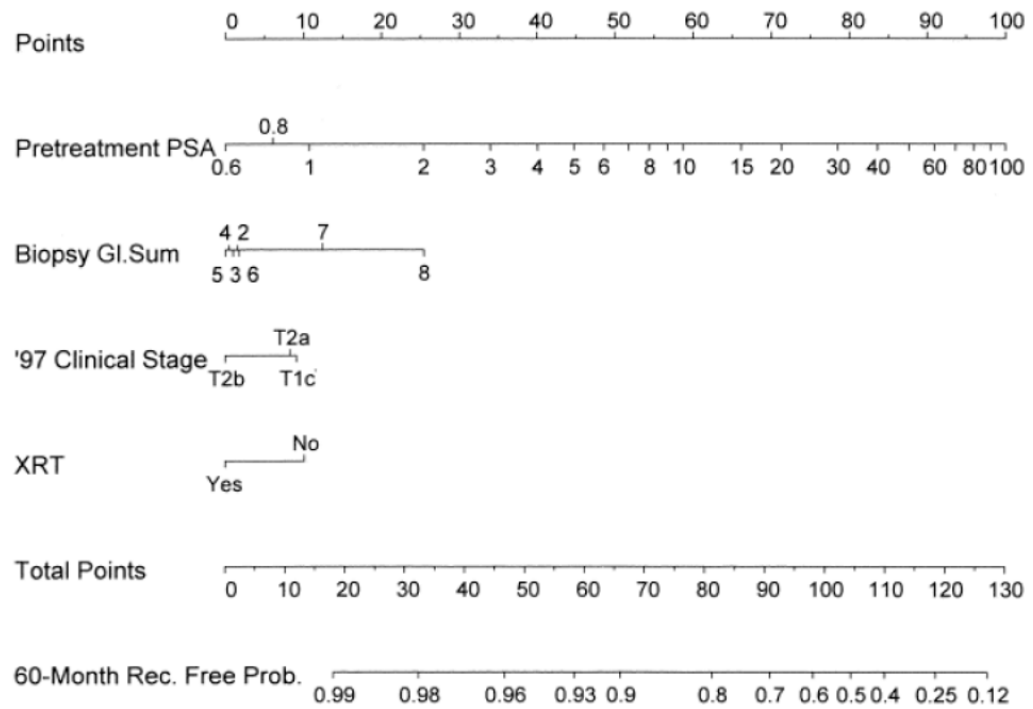


Fig 5. Pre-treatment nomogram for predicting 5-year biochemical recurrence-free probability after permanent prostate brachytherapy without neo-adjuvant androgen ablative therapy. Reprinted with permission from Kattan *et al* [84].

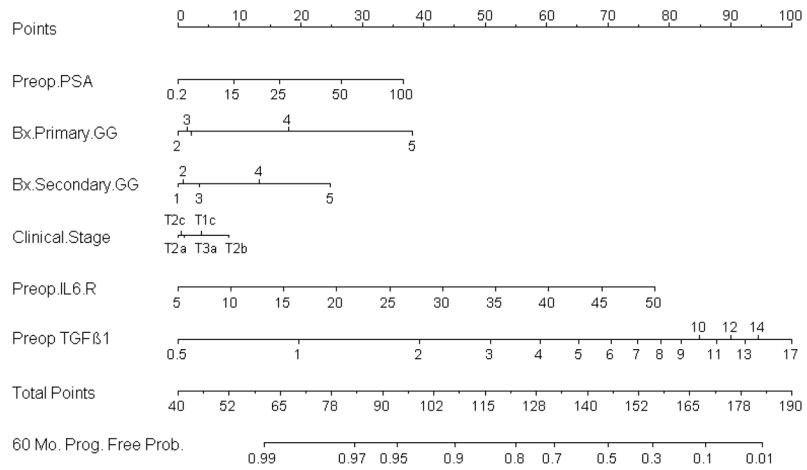


Fig 6. Pre-treatment nomogram for predicting 5-year biochemical recurrence-free probability after radical prostatectomy including pre-operative plasma levels of transforming growth factor β 1 and interleukin-6 soluble receptor. Reprinted with permission from Kattan et al [100].

Table 1

Prostate biopsy nomograms for prediction of prostate cancer in the initial biopsy

Reference	Year	Prediction form	No of Patients	Variables	Mean # of cores	Cancer detection	Discrimination	Validation
Babaian et al. [113]	1998	Risk group	151	Age, creatinine phosphokinase isoenzyme activity, prostatic acid phosphatase, PSA	6	24%	74%	Not performed
Eastham et al. [51]	1999	Probability nomogram development	700	Age, race, DRE, PSA (0–4 ng/mL)	6	9%	75%	Internal
Virtanen et al. [114]	1999	Neural network	212	Percent free PSA, DRE, heredity	Not available	25%	81%	Not performed
Finne et al. [115]	2000	Neural network	656	Percent free PSA, PSA, DRE, TRUS	Not available	23%	Not available	Not performed
Hominger et al. [116]	2001	Neural network	3474	Age, PSA, percent free PSA, DRE, TRUS, PSA density, PSA density of transition zone, transition zone volume	Not available	Not available	Not available	Not performed
Kalra et al. [117]	2003	Neural network	348	Age, ethnicity, heredity, IPSS, DRE, PSA, complexed PSA	6	Not available	83%	Not performed
Garzotto et al. [118]	2003	Probability nomogram development	1239	Age, race, family history, referral indications, prior vasectomy, DRE, PSA (≤ 10 ng/mL), PSA density, TRUS findings	6.7 (6–13)	24%	73%	Not performed
Finne et al. [119]	2004	Neural network	1775	DRE, percent free PSA, TRUS, PSA	Not available	22%	76%	Not performed
Karakiewicz et al. [120]	2005	Probability nomogram development	6469	Age, DRE, PSA, percent free PSA	6	35%–42%	77%	Internal and external

Reference	Year	Prediction form	No of Patients	Variables	Mean # of cores	Cancer detection	Discrimination	Validation
Porter et al. [121]	2005	Neural network	3814	Age, PSA, gland volume, PSA density, DRE, TRUS	6	27–42%	72–75%	Internal and external
Suzuki et al. [122]	2006	Probability nomogram development	834	Age, PSA, percent free PSA, prostate volume, DRE	≥6	29%	82%	Internal
Thompson et al. [55]	2006	Probability nomogram development	5519	Age, race, family history of prostate cancer, PSA level, PSA velocity, DRE result, and previous prostate biopsy	6	21.9%	65.5%	Internal and external [54]
Chun et al. [52]	2007	Probability nomogram validation [120] and development	2900	Age, DRE, PSA, percent free PSA, sampling density*	11 (10–20)	41%	77%	Internal and external
Nam et al. [53]	2007	Probability nomogram development	3108	Age, ethnicity, family history, urinary symptoms, PSA, percent free PSA, and DRE	8 (6–15)	42%	Any cancer: 62% High-grade cancer: 69%	Internal

DRE = digital rectal examination; PSA = prostate-specific antigen; TRUS = transrectal ultrasound of the prostate; HGPPIN = high-grade intraepithelial neoplasia; ASAP = atypical small acinar proliferation of prostate; IPSS = International Prostate Symptom Score

* Sampling density = ratio of TRUS-derived total gland volume to the number of cores at biopsy

Table 2
Prostate biopsy nomograms for prediction of prostate cancer in settings other than initial biopsy

Reference	Year	Prediction form	No of Patients	Variables	Median # of previous biopsy sessions	Mean # of cores	Cancer detection	Discrimination	Validation
Repeat biopsy									
O'Dowd et al. [123]	2000	Probability nomogram development	813	Age, initial biopsy diagnosis, PSA, percent free PSA	Not available	Not available	29%	70%	Not performed
Lopez-Corona et al. [56]	2003	Probability nomogram development	343	Age, DRE, number previous negative biopsies, HGPIN history, ASAP history, PSA, PSA slope, family history, months from initial negative biopsy	2.9 (2-12)	9.2 (6-22)	20%	70%	Internal
Remzi et al. [124]	2003	Neural network	820	PSA, percent free PSA, TRUS, PSA density, PSA density of the transition zone, transition zone volume	Not available	8	10%	83%	Not performed
Yanke et al. [57]	2005	Probability nomogram validation [56]	230 (356 biopsies)	Age, DRE, number previous negative	2.6 (2-7)	17.9 (12-54)	34%	71%	Internal

Reference	Year	Prediction form	No of Patients	Variables	Median # of previous biopsy sessions	Mean # of cores	Cancer detection	Discrimination	Validation
Chun et al. [58]	2007	Probability nomogram development	2393	Age, DRE, PSA, biopsies, HGPIN history, ASAP history, PSA, PSA slope, family history, months from initial negative biopsy, months from previous negative biopsy	1.5 (1-7)	11 (10-24)	30%	76%	Internal and external
Saturation biopsy									
Walz et al. [125]	2006	Probability nomogram development	161	Age, PSA, percent free PSA, prostate and BPH volume, PSA doubling time, PSA density of the transition zone, number of previous biopsy sessions, number of cores at	2.5 (2-5)	24.5 (20-32)	41%	75%	Internal

Reference	Year	Prediction form	No of Patients	Variables saturation biopsy	Median # of previous biopsy sessions	Mean # of cores	Cancer detection	Discrimination	Validation
Mixed – Initial and repeat biopsy									
Snow et al. [17]	1994	Neural network	1787	Age, change on PSA, DRE, PSA, TRUS	Not available	6	34%	87%	Not performed
Carlson et al. [126]	1998	Probability table	3773	Age, PSA, Percent free PSA	Not available	6	33%	Not available	Internal
Djavan et al. [127]	2002	Neural network	272	PSA density of the transition zone, percent free PSA, PSA density, TRUS (PSA: 2.5–4.0 ng/mL)	Not available	8	24%	88%	Not performed
			974	PSA density of the transition zone, percent free PSA, PSA velocity, transition zone volume, PSA, PSA density (PSA: 4.0–10.0 ng/mL)	Not available	8	35%	91%	Not performed
Stephan et al. [128]	2002	Neural network	1188	Age, DRE, PSA, percent	Not available	Not available	61%	86%	Not performed

Reference	Year	Prediction form	No of Patients	Variables	Median # of previous biopsy sessions	Mean # of cores	Cancer detection	Discrimination	Validation
Porter et al. [129]	2002	Neural network	319	Age, PSA, gland volume, TRUS, DRE, previous negative biopsy, African-American race	Not available	9.7 (6–10)	39%	76%	Not performed
Matsui et al. [130]	2004	Neural network	228	PSA density, DRE, age, TRUS	Not available	10–12	26%	73%	Not performed
Beneccchi [131]	2006	Neural network	1030	Age, PSA, percent free PSA	Not available	6–12	19%	80%	Not performed
Yanke et al. [132]	2006	Probability nomogram	8851	Age, race, PSA, DRE, number of cores	Not available	6–13	27–38%	75%	Internal

DRE = digital rectal examination; PSA = prostate-specific antigen; TRUS = transrectal ultrasound prostate; HGPIN = high-grade intraepithelial neoplasia; ASAP = atypical small acinar proliferation of prostate.

* Sampling density = ratio of TRUS-derived total gland volume by the number of cores at biopsy

Table 3
 Prediction of pathologic stage in men treated with radical prostatectomy for clinically localized prostate cancer

Reference	Year	Prediction form	Outcome	No of Patients	Variables	Discrimination	Validation
Narayan et al. [133]	1995	Probability graph	Pathologic Stage	813	Biopsy based stage, biopsy Gleason sum, PSA	Not available	Not performed
Partin et al. [18, 19,134]	1993, 1997, and 2007	Probability table	Pathologic Stage	703 and 4133	Biopsy Gleason sum, clinical stage, PSA	Internal: 72% External: 84%	External [135] and updated [19,61,136]
Epstein et al. [137]	1994	Risk group	Clinically indolent cancer defined as pathologically organ confined, tumor volume ≤ 0.2 cc, Gleason sum < 7	157	Biopsy Gleason sum, millimeter core with cancer, PSA density, no adverse pathologic findings on needle biopsy	Not available	External [138]
Goto et al. [139]	1996	Risk group	Clinically indolent cancer defined as pathologically organ confined, tumor volume ≤ 0.5 cc, Gleason sum < 7	569	PSA density, maximal millimeter cancer in any core	Not available	Not performed
Kattan et al. [70]	2003	Probability nomogram development	Clinically indolent cancer defined as pathologically organ confined, tumor volume ≤ 0.5 cc, no Gleason grade 4 or 5	409	PSA, primary and secondary biopsy Gleason sum PSA, primary and secondary biopsy Gleason sum, percent positive cores, TRUS volume PSA, clinical stage, primary and secondary biopsy Gleason sum,	64% 74% 79%	Internal and external [29] Internal and external [29] Internal and external [29]

Reference	Year	Prediction form	Outcome	No of Patients	Variables	Discrimination	Validation
Chun et al. [140]	2006	Probability nomogram development	Gleason upgrading between biopsy and radical prostatectomy	2982	TRUS volume, millimeter core with cancer, millimeter core without cancer	80%	Internal
Chun et al. [141]	2006	Probability nomogram development	Significant Gleason upgrading between biopsy and radical prostatectomy	4789	PSA, clinical stage, primary and secondary biopsy Gleason sum	76%	Internal
Steuber et al. [142]	2006	Probability nomogram development	Tumor location: transition versus peripheral zone	945	PSA, biopsy Gleason sum, positive biopsy cores at mid-prostate only, number of positive biopsy cores at base, cumulative percent biopsy tumor volume	77%	Internal
Peller et al. [143]	1995	Probability table	Tumor volume	102	Biopsy Gleason sum, number positive sextant cores, PSA	Not available	Not performed
Ackerman et al. [144]	1993	Probability formula	Surgical margin positivity	107	Number positive sextant cores, PSA density	70%	Not performed
Rabbani et al. [145]	1998	Probability graph	Surgical margin positivity	242	Androgen deprivation, number ipsilateral	Not available	Not performed

Reference	Year	Prediction form	Outcome	No of Patients	Variables	Discrimination	Validation
Bostwick et al. [146]	1996	Probability graph	Capsular penetration	314	Biopsy Gleason sum, percent cancer in biopsy cores, PSA	78%	Not performed
Gamito et al. [147]	2000	Neural network	Capsular penetration	4133	Age, race, PSA, PSA velocity, Gleason sum, clinical stage	30–76%	External
Gilliland et al. [148]	1999	Probability graph	Extracapsular extension	3826	Age, biopsy Gleason sum, PSA	63%	Not performed
Ohori et al. [62]	2004	Probability nomogram development	Side-specific extracapsular extension	763	PSA, clinical stage, side-specific biopsy Gleason sum, side-specific percent positive cores, side-specific percent of cancer in cores	81%	External [63]
Steuber et al. [63]	2006	Probability nomogram development	Side-specific extracapsular extension	1118	PSA, clinical stage, biopsy Gleason sum, percent positive cores, percent of cancer in positive cores	84%	Internal
Veltri et al. [149] Haese et al. [150]	2001, 2003	Ordinal logistic regression and neural network	Organ confined disease	1287	Age, PSA, No of cores positive, highest Gleason score, average % tumor involvement per core,	93–98.6%	External

Reference	Year	Prediction form	Outcome	No of Patients	Variables	Discrimination	Validation
Badalament et al. [151]	1996	Probability formula	Organ confined disease	192	Biopsy Gleason sum, involvement of greater than 5% of base with or without apex biopsy, nuclear grade, PSA, total percent tumor involvement	86%	Not performed
Bostwick et al. [146]	1996	Probability graph	Seminal vesicle invasion	314	Biopsy Gleason sum, percent cancer in cores, PSA	76%	Not performed
Pisansky et al. [152]	1996	Probability graph	Seminal vesicle invasion	2953	Biopsy Gleason primary grade, clinical stage, PSA	80%	Internal
Koh et al. [64]	2003	Probability nomogram development	Seminal vesicle invasion	763	PSA, clinical stage, primary and secondary Gleason sum, and percent of cancer at the base	88%	Internal
Baccala et al. [153]	2007	Probability nomogram development	Seminal vesicle invasion	6740	Age, PSA, Biopsy Gleason sum, clinical stage	80%	Internal
Gallina et al. [65]	2007	Probability nomogram development	Seminal vesicle invasion	896	PSA, clinical stage, biopsy Gleason sum, percent	79%	Internal and external

Reference	Year	Prediction form	Outcome	No of Patients	Variables	Discrimination	Validation
Ackerman et al. [144]	1993	Probability formula	Lymph node invasion assessed with limited pelvic lymphadenectomy	107	Number positive sextant cores, PSA	94%	Not performed
Roach et al. [154]	1994	Probability graph	Lymph node invasion assessed with limited pelvic lymphadenectomy	212	Biopsy Gleason sum, PSA	Not available	Not performed
Bluestein et al. [155]	1994	Probability graph	Lymph node invasion assessed with limited pelvic lymphadenectomy	816	Biopsy Gleason sum, clinical stage, PSA	82%	Internal
Battello et al. [156]	2001	Neural network	Lymph node invasion assessed with limited pelvic lymphadenectomy	6454	Biopsy Gleason sum, clinical stage, PSA	77–81%	Internal and external
Cagiannos et al. [66]	2003	Probability nomogram development	Lymph node invasion assessed with limited pelvic lymphadenectomy	5510	PSA, clinical stage, biopsy Gleason sum	76%	Internal
					PSA, clinical stage, biopsy Gleason sum, institution	78%	Internal
Briganti et al. [67, 157, 158]	2006, 2007	Probability nomogram development	Lymph node invasion assessed with extended pelvic lymphadenectomy (≥ 10 nodes)	602 [67]	PSA, clinical stage, biopsy Gleason sum	76%	Internal
				781 [157]	PSA, clinical stage, biopsy Gleason sum, number of lymph nodes	79%	Internal
				278 [158]	PSA, clinical stage, biopsy Gleason sum, percentage positive biopsy cores	83%	Internal

PSA = prostate-specific antigen; TRUS = transrectal ultrasound;

Table 4

Pre- and post-operative prediction of biochemical recurrence at 2–10 years in men treated with radical prostatectomy

Reference	Year	Prediction form	Biochemical recurrence, years	No of Patients	Variables	Discrimination	Validation
Snow et al. [17]	1994	Neural network	Not available	240	Age, PSA, clinical stage, biopsy Gleason grade, potency	90%	Not performed
Kattan et al. [12]	1998	Probability nomogram development	5	983	Biopsy primary and secondary Gleason grade, clinical stage, PSA	Internal: 74% External: 65–83%	Internal and external [30, 72,73,159]
D'Amico et al. [15]	1999	Probability table	2	892	Biopsy Gleason sum, clinical stage, PSA	Not available	Internal
Graefen et al. [160]	1999	Probability graph	3.5	315	Biopsy Gleason sum, number of positive cores, PSA	Not available	Not performed
D'Amico et al. [16]	2000	Probability graph	2	977	Biopsy Gleason sum, endorectal coil magnetic resonance imaging T-stage, PSA, percent positive biopsy cores	Not available	Internal
Tewari et al. [161]	2001	Neural network	3.5	1400	Age, race, PSA, clinical staging, biopsy Gleason sum	83%	Not performed
D'Amico et al. [13, 14]	1998, 2002	Probability graph	4	823	Biopsy Gleason sum, clinical stage, PSA, percent positive biopsy cores	80%	Internal and external [72, 162]
Cooperberg et al. [163]	2005	Probability graph	3 and 5	1439	Age, PSA, biopsy Gleason sum, clinical stage, percent positive biopsy	Internal: 66% External: 68–81%	Internal and external [164,165]
Stephenson et al. [37]	2006	Probability nomogram development	10	1978 and 1545	PSA, clinical stage, biopsy Gleason sum, year of surgery,	76–79%	Internal and external

Reference	Year	Prediction form	Biochemical recurrence, years	No of Patients	Variables	Discrimination	Validation
Post-operative							
Bauer et al. [166]	1998	Probability formula	5	378	Race, PSA, Gleason sum, organ confined status	Not available	External [167]
D'Amico et al. [13]	1998	Probability graph	2	862	Pathologic stage, PSA, Gleason sum, surgical margin status	Not available	Not performed
Graefen et al. [160]	1999	Probability graph	3.5	318	Pathologic stage, volume Gleason grade 4/5	Not available	Not performed
Potter et al. [168]	1999	Neural network	5	214	Gleason sum, extraprostatic extension, surgical margin status, age, DNA ploidy, and quantitative nuclear grade	94%	Internal
Kattan et al. [11]	1999	Probability nomogram development	5	996	PSA, Gleason sum, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margin status	Internal: 89% External: 77–83%	Internal and external [74, 78,169]
Stamey et al. [170]	2000	Probability formula	Unknown	326	PSA, percent Gleason grade 4/5, volume largest cancer, vascular invasion, prostate weight, percent intraductal cancer, lymph node invasion	Not available	Not performed
McAleer et al. [171]	2005	Probability graph	7	2417	Gleason grade, stage, margin status, dichotomized	Not available	Internal

Reference	Year	Prediction form	Biochemical recurrence, years	No of Patients	Variables	Discrimination	Validation
Stephenson et al. [36]	2005	Probability nomogram development	10	1881, 1782, and 1357	PSA (cut point 10 ng/mL), PSA, Gleason sum, extracapsular extension, seminal vesicle invasion, lymph node invasion, surgical margin status	78–86%	Internal and external
Suardi et al. [36]	2008	Probability nomogram development	5, 10, 15, and 20	601 (development), 2963 and 3178 (external)	Gleason sum, pathologic stage, surgical margin status, type of surgery, adjuvant radiotherapy	Internal: 77–81% External: 77–86%	Internal and external

Table 5
Pre-treatment prediction of biochemical recurrence at 2–10 years in men treated with radiotherapy

Reference	Year	Prediction form	Biochemical recurrence, years	No of Patients	Variables	Discrimination	Validation
External beam radiotherapy							
Duchesne et al. [172]	1996	Risk group	5	85	PSA, biopsy Gleason sum	Not available	Not performed
Pisansky et al. [173]	1997	Risk group	5	500	Biopsy Gleason sum, clinical stage, PSA	Not available	Internal
Zagars et al. [174]	1997	Probability graph	6	938	PSA, biopsy Gleason sum, clinical stage	Not available	Not performed
D'Amico et al. [15]	1999	Probability table	2	762	Biopsy Gleason sum, clinical stage, PSA	Not available	Not performed
Shipley et al. [175]	1999	Probability table	5	1607	Biopsy Gleason sum, clinical stage, PSA	Not available	Not performed
Kattan et al. [81]	2000	Probability nomogram development	5	1042 and 1030	PSA, biopsy Gleason sum, clinical stage, neoadjuvant androgen deprivation therapy, radiation dose delivered	73%	Internal
D'Amico et al. [82,83]	1998, 2002	Probability graph	5	766	Biopsy Gleason sum, clinical stage, PSA, treatment modality	Not available	Internal
Brachytherapy							
D'Amico et al. [83]	1998	Probability graph	5	218	Biopsy Gleason sum, clinical stage, PSA, neo-adjuvant therapy	Not available	Not performed
Ragde et al. [176]	1998	Risk group	10	98	Age, biopsy Gleason sum, clinical stage, PSA, 45 Gy external beam radiotherapy	76%	Internal
Kattan et al. [84]	2001	Probability nomogram development	5	920 and 1827 and 765	Biopsy Gleason sum, clinical stage, PSA, co-administration of	61–64%	Internal and external

Reference	Year	Prediction form	Biochemical recurrence, years	No of Patients	Variables	Discrimination	Validation
					external beam radiotherapy		

Table 6

Prediction of metastasis and survival

Reference	Year	Prediction form	Patient population	Outcome (years)	No of Patients	Variables	Discrimination	Validation
Partin et al. [177]	1994	Probability graph	Radical prostatectomy	Local versus distant recurrence	1058	PSA velocity, Gleason sum, pathologic stage	Not available	Not performed
Pound et al. [75]	1999	Probability table	Biochemical recurrence after radical prostatectomy	Metastasis (7 years after biochemical recurrence)	315	PSA doubling time, Gleason sum, time to biochemical recurrence	56%	Not performed
D'Amico et al. [178]	2003	Probability graph	Radical prostatectomy	Prostate cancer-specific mortality (8)	4946	Biopsy Gleason sum, clinical stage, PSA	Not available	Internal
Dotan et al. [86]	2005	Probability nomogram development	Biochemical recurrence after radical prostatectomy	Positive bone scan	239	Pre-treatment PSA, surgical margin status, seminal vesicle invasion, Gleason sum, trigger PSA, extracapsular extension, PSA slope, PSA velocity	93%	Internal
Freedland et al. [76]	2005	Probability table	Biochemical recurrence after radical prostatectomy	Cancer-specific survival (10 years after biochemical recurrence)	379	PSA doubling time, Gleason sum, time from surgery to biochemical recurrence	59%	Not performed
D'Amico et al. [179,180]	2002, 2003	Probability graph	External beam radiotherapy	Prostate cancer-specific mortality (10)	381	Biopsy Gleason sum, clinical stage, PSA, percent positive biopsy	Not available	Internal
					94	Time to PSA failure, post-treatment PSA doubling time, timing of salvage hormonal therapy.		
D'Amico et al. [178]	2003	Probability graph	External beam radiotherapy	Prostate cancer-specific mortality (8)	2370	Biopsy Gleason sum, clinical stage, PSA	Not available	Internal
Kattan et al. [85]	2003	Probability nomogram development	External beam radiotherapy	Metastasis (5)	1677 and 1626	PSA, clinical stage, biopsy Gleason sum	81%	Internal and external
Slovin et al. [87]	2005	Probability nomogram development	External beam radiotherapy	Metastasis (1-2)	148	Baseline PSA, PSA doubling time, Pathologic T stage, Gleason sum	69%	Not performed
Zhou et al. [181]	2005	Probability graph	External beam radiotherapy	Prostate cancer-specific mortality (5)	661	PSA doubling time, biopsy Gleason sum	Not available	Internal
Stephenson et al. [182]	2007	Probability nomogram development	Salvage radiotherapy for biochemical recurrence after radical prostatectomy	Biochemical recurrence after radiotherapy (7 years after biochemical recurrence)	1540	Prostatectomy PSA, Gleason sum, seminal vesicle invasion, extracapsular extension, surgical margin status, lymph node	69%	Internal

Reference	Year	Prediction form	Patient population	Outcome (years)	No of Patients	Variables	Discrimination	Validation
Zhou et al. [181]	2005	Probability graph	Biochemical recurrence after radical prostatectomy	Prostate cancer-specific mortality (5)	498	PSA doubling time	Not available	Internal
Slovin et al. [87]	2005	Probability nomogram development	Biochemical recurrence after radical prostatectomy or radiotherapy	Metastasis (1–2)	148	Baseline PSA, PSA doubling time, Pathologic T stage, Gleason sum	69%	Not performed
Svatek et al. [183]	2006	Probability nomogram development	Androgen-independent prostate cancer	Prostate cancer-specific mortality (1–5)	129	PSA at initiation of androgen-deprivation therapy, PSA doubling time, nadir (SA on androgen-deprivation therapy, time from androgen-deprivation therapy to androgen-independent prostate cancer	81%	Internal
Smaletz et al. [90]	2002	Probability nomogram development	Men with progressive metastatic prostate cancer after castration	Overall survival (1–2)	409 and 433	Age, Karnofsky performance index, hemoglobin, PSA, lactic dehydrogenase, alkaline phosphatase, albumin	71%	Internal and external
Porter et al. [89]	2007	Probability nomogram development	Men on androgen-deprivation therapy after radical prostatectomy	Prostate cancer-specific mortality (2–5)	66	Pathologic T stage, Gleason sum, surgical margin status, age at androgen-deprivation therapy, recurrence type	66%	Internal
Halabi et al. [91]	2003	Probability nomogram development	Metastatic hormone-refractory prostate cancer	Overall survival (1–2)	1101	Lactate dehydrogenase, PSA, alkaline phosphatase, Gleason sum, Eastern Cooperative Oncology Group performance status, hemoglobin, presence of visceral disease	68%	Internal and external
Armstrong et al. [88]	2007	Probability nomogram development	Hormone-refractory prostate cancer	Overall survival (1, 2, and 5)	1006	Liver metastases, number of metastatic sites, clinically significant pain, Karnofsky performance status, type of progression (measurable progression and bone scan progression), pretreatment PSA doubling time, PSA, tumor grade, alkaline phosphatase, and hemoglobin	69%	Internal

Table 7

Prediction of life expectancy in men with clinically localized prostate cancer

Reference	Year	Prediction form	Outcome	No of Patients	Variables	Discrimination	Validation
Albertson et al. [95]	1996	Probability formula	Overall survival (10 years)	451	Age, Gleason sum and index of coexistent disease category	71%	Not performed
Tewari et al. [93]	2004	Probability graph	Overall survival (10 years)	6149	Age, race, comorbidity, PSA, Gleason sum, treatment type	63%	Not performed
Cowen et al. [94]	2006	Probability nomogram development	Life expectancy (5–15 years)	506	Age, Charlson comorbidity index, presence of angina, systolic blood pressure, body mass index, smoking, marital status, PSA < Gleason sum, clinical stage, treatment type (radical prostatectomy vs radiotherapy vs other)	73%	Internal
Walz et al. [97]	2007	Probability nomogram development	Life expectancy (10 years)	9131 (5,955 treated with radical prostatectomy and 3,176 with external beam radiotherapy)	Age, Charlson comorbidity index, treatment type (radical prostatectomy vs external beam radiotherapy)	84.3%	Internal

Table 8

Prediction of specific pathologic features or biochemical recurrence in men treated with radical prostatectomy for clinically localized prostate cancer based on novel variables

Reference	Year	Prediction form	Novel variable	Outcome	No of Patients	Variables	Discrimination	Validation
Pre-operative								
Wang et al. [184]	2006	Probability nomogram development	MRI and magnetic resonance spectroscopic imaging	Lymph node invasion	411	MRI variables and Partin probability table [18]	89%	Internal
Wang et al. [106]	2007	Probability nomogram development	MRI and magnetic resonance spectroscopic imaging	Seminal vesicle invasion	573	MRI variables and pre-operative Kattan probability nomogram [12]	87%	Internal
Shukla-Dave et al. [107]	2007	Probability nomogram development	MRI and magnetic resonance spectroscopic imaging	Insignificant cancer (organ-confined cancer of ≤ 0.5 cm ³ with no poorly differentiated elements)	220	Pretreatment PSA, clinical stage, biopsy cores positive, pretreatment MRI volume of prostate, and overall MRI/MRSI score	85%	Internal
Kattan et al. [100]	2003	Probability nomogram development	Plasma levels of transforming growth factor β 1 and interleukin 6 soluble receptor	Biochemical recurrence	714	Preoperative plasma transforming growth factor β 1 and interleukin 6 soluble receptor and pre-operative Kattan probability nomogram [12]	83%	Internal
Shariat et al. [185]	2007	Probability nomogram development	Plasma levels of plasminogen activator inhibitor 1	Biochemical recurrence	429	Preoperative plasma plasminogen activator inhibitor 1 and pre-operative Kattan probability nomogram [12]	79%	Internal
Post-operative								
Stephenson et al. [101]	2005	Probability nomogram development	Gene expression based on oligonucleotide microarrays	Biochemical recurrence	79	Gene expression signatures and post-operative Kattan probability nomogram [11]	89%	Internal

MRI = magnetic resonance imaging