

## REVIEW

# Formalized prediction of clinically significant prostate cancer: is it possible?

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Greater understanding of the biology and epidemiology of prostate cancer in the last several decades have led to significant advances in its management. Prostate cancer is now detected in greater numbers at lower stages of disease and is amenable to multiple forms of efficacious treatment. However, there is a lack of conclusive data demonstrating a definitive mortality benefit from this earlier diagnosis and treatment of prostate cancer. It is likely due to the treatment of a large proportion of indolent cancers that would have had little adverse impact on health or lifespan if left alone. Due to this overtreatment phenomenon, active surveillance with delayed intervention is gaining traction as a viable management approach in contemporary practice. The ability to distinguish clinically insignificant cancers from those with a high risk of progression and/or lethality is critical to the appropriate selection of patients for surveillance protocols versus immediate intervention. This chapter will review the ability of various prediction models, including risk groupings and nomograms, to predict indolent disease and determine their role in the contemporary management of clinically localized prostate cancer.

*Asian Journal of Andrology* (2012) 14, 349–354; doi:10.1038/aja.2011.140; published online 27 February 2012

**Keywords:** prediction model; prostate cancer; prostatic neoplasms; screening

## INTRODUCTION

The management of prostate cancer has evolved significantly over the past several decades. The introduction of prostate-specific antigen (PSA) screening led to a stage migration whereby the vast majority of patients are now diagnosed with organ-confined prostate cancer.<sup>1,2</sup> We have ever more effective means of achieving local control of disease and even patients with metastatic disease have greater treatment options than ever before. Indeed, the likelihood of cure with definitive treatment has increased, while there has been a concomitant reduction in the mortality rate.<sup>3</sup>

And yet, despite these advances, prostate cancer remains the second most common cause of cancer-specific death among men in the United States.<sup>4</sup> Furthermore, there is controversy regarding whether or not the early detection of prostate cancer through PSA screening has actually saved lives. Interim data from two long-term screening studies<sup>5,6</sup> were published in 2009 and demonstrated conflicting outcomes. The Prostate, Lung, Colorectal, and Ovarian screening trial found no significant difference in prostate cancer death rates between men who were screened and those who were not,<sup>5</sup> while the European Randomized Study of Screening for Prostate Cancer reported a 20% reduction in the mortality rate of men in the screened cohort.<sup>6</sup>

The observations suggest that current strategies of cancer detection and treatment are disproportionately targeting clinically insignificant cancers that pose little or no threat to the health or longevity of the patient. Indeed, an analysis of Surveillance Epidemiology and End Results data regarding prostate cancer incidence between 1986 and 2005 found that PSA screening resulted in the additional detection and

treatment of more than a million men.<sup>7</sup> Assuming that the reported decline in prostate cancer mortality during this same period was due to screening, the authors found that nearly 20 men had to be diagnosed and treated for each death that was prevented. This has been further corroborated by the aforementioned Prostate, Lung, Colorectal, and Ovarian and European Randomized Study of Screening for Prostate Cancer which both reported very low prostate cancer death rates, suggesting that the majority of prostate cancer is unlikely to progress. The conclusion, then, is that the majority of men who are diagnosed with prostate cancer are unlikely to benefit from treatment.

The ethical and economic implications of the overdiagnosis and overtreatment of clinically insignificant prostate cancer are profound. Men with indolent cancers presumably would not benefit from active treatment and may suffer significant harm in the form of treatment-related complications, such as impotence and incontinence. The cost-effectiveness of current screening regimens has also been called into question. Based on the aforementioned data from the Surveillance Epidemiology and End Results, Prostate, Lung, Colorectal, and Ovarian and European Randomized Study of Screening for Prostate Cancer, the number of men who must be screened and treated in order to prevent just one cancer-related death is substantial. The costs associated with such a high number of unnecessary treatments are likely adding greater burden to an already overstretched healthcare system.

This seemingly indiscriminate application of treatment among contemporary men diagnosed with prostate cancer is largely due to an inability to foresee the natural history of any given cancer. Because the course of prostate cancer can vary significantly between individual

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Received: 3 October 2011; Revised: 4 November 2011; Accepted: 4 November 2011; Published online: 27 February 2012

patients, there is no one treatment approach that is appropriate for all men. Predicting tumor biology allows identification of potentially lethal cancers and facilitates rational patient selection for active surveillance versus definitive therapy. In this chapter, we review the accuracy and utility of currently available clinical parameters and algorithms in the prediction of clinically significant prostate cancer.

### HOW IS CLINICALLY (IN)SIGNIFICANT DISEASE DEFINED?

One could reasonably propose that clinically significant prostate cancer is that which has a high likelihood of progressing, metastasizing and/or causing mortality within the lifespan of the patient. In other words, it is disease that adversely impacts quality of life and longevity and merits immediate definitive treatment. In contrast, insignificant cancers that do not fulfill these criteria would presumably be suitable for surveillance with deferred treatment. However, more objective and definitive criteria are required in order to facilitate patient counseling and selection for active surveillance protocols, allowing reproducible protocols across clinical practice.

Accurately defining clinically (in)significant disease has been problematic for several reasons. First, the most applicable end points that reflect biological significance, such as development of metastatic disease and cancer-specific mortality, are exceedingly difficult to reach and therefore not assessed in most studies. As a result, surrogate end points with questionable correlation to actual disease course (e.g., biochemical relapse) are used instead. Second, the ideal dataset (e.g., one that contains a large number of men with newly diagnosed prostate cancer who are followed long term without intervention until progression or death) does not exist due to obvious ethical and logistical constraints.

Third, the traditional definition of insignificant prostate cancer, i.e., organ-confined disease with a volume <0.5 ml and a Gleason sum  $\leq 6$ , depends on pathological data that are only available if the patient actually undergoes treatment (e.g., prostatectomy). There is admittedly a multitude of clinical parameters that are prognostic for prostate cancer progression and aggressiveness, including tumor-specific markers (e.g., PSA, Gleason grade, tumor volume), patient-specific factors (e.g., age and race) and biological/genetic markers (PCA3, Ki-67, p53). Unfortunately, there is no single pretreatment clinical marker among these that predicts prostate cancer aggressiveness and lethality with perfect accuracy.

To this end, investigators have developed risk grouping schema that incorporate multiple clinical prognostic factors, including PSA, clinical stage, biopsy Gleason grade and other biopsy parameters. Although most currently available algorithms consider the same group of variables in assigning risk to patients, there is currently no set of pretreatment criteria that is universally accepted and utilized in clinical practice.

### Risk groupings in the prediction of insignificant disease

Perhaps the most widely used risk grouping for prediction of clinically insignificant disease is based upon the Epstein criteria, which were based on PSA and biopsy pathological data. The original criteria include clinical stage T1c, PSA density <0.15, Gleason score  $\leq 6$ , no more than two cores with cancer and no cores with >50% cancer involvement. The initial 1994 study reported that insignificant cancers could be predicted with up to 80% accuracy.<sup>8</sup> The criteria were validated in a contemporary cohort of patients and shown to accurately predict organ-confined disease in almost 92% of patients.<sup>9</sup> There are a number of other schema that have been published by various groups seeking to identify patients with organ-confined disease and a low risk of progression that would be suitable for active surveillance (Table 1).

### Limitations of definitions based on risk-groupings

An important question about the utility of these risk groupings surrounds what they actually predict. For example, the Epstein criteria have been shown to be predictive of organ-confined disease, but organ-confinement may not necessarily be equivalent to biological indolence. Lee and colleagues from the Cleveland Clinic validated the Epstein criteria in their cohort of low-risk patients (Gleason score  $\leq 6$ ) treated with radical prostatectomy and found that the criteria underestimated the presence of Gleason 7 cancer (38% of patients) and extra-prostatic disease (7% of patients).<sup>10</sup>

Similarly, validation studies based on international cohorts have shown that the Epstein criteria can underestimate the aggressiveness of disease in as many as a third of men with prostate cancer, as demonstrated by the presence of pathological Gleason score  $\geq 7$  or non-organ-confined disease.<sup>11,12</sup> Moreover, a recent systematic review of the validation literature on the Epstein criteria reported a substantial reduction in the accuracy of the criteria for predicting insignificant cancer or organ-confined disease in more contemporary cohorts of men (i.e., post-2005).<sup>13</sup>

Other risk-stratification schemata have also demonstrated similar shortcomings to the Epstein criteria. Suardi and colleagues<sup>14</sup> compared the predictive accuracy of the risk definitions summarized in Table 1 in a cohort of nearly 5000 German and Italian men who underwent radical prostatectomy. The concordance between pretreatment and post-treatment risk classification was then determined. If Gleason scores  $\geq 7$  were considered high-risk, then the percentage of patients who were misclassified as low-risk prior to surgery and subsequently upgraded to high-risk disease based on post-surgical data ranged from 30% to 56% among the six risk definitions. When high-risk disease was restricted to cancers with a Gleason score  $\geq 8$ , the percentages of misclassified patients ranged from 7% to 27%.

As suggested by these data, grouping is an inefficient use of the available data and tends to reduce the predictive accuracy of a prognostic model. The predictive capability of risk groupings is based on

**Table 1 Risk grouping schema for low-risk/insignificant prostate cancer**

Scheme	Criteria
Epstein <i>et al.</i> , <sup>8</sup> 1994	Clinical stage T1c; PSA density <0.15, biopsy Gleason score $\leq 6$ ; no more than two cores with cancer, or cancer involving no more than 50% of any core on a prostate biopsy
D'Amico and Coleman, <sup>33</sup> 1996	Clinical stage T1c–T2a; PSA $\leq 10$ ng ml <sup>-1</sup> ; biopsy Gleason score $\leq 6$
Choo <i>et al.</i> , <sup>34</sup> 2002	Clinical stage T1b–T2b; PSA $\leq 15$ ng ml <sup>-1</sup> ; biopsy Gleason score $\leq 7$
Hardie <i>et al.</i> , <sup>35</sup> 2005	Clinical stage T1–2; PSA $\leq 20$ ng ml <sup>-1</sup> ; biopsy Gleason score $\leq 7$
Klotz, <sup>36</sup> 2005	Clinical stage T1c–T2a; PSA $\leq 10$ ng ml <sup>-1</sup> for patients of age under 70 years and $\leq 15$ ng ml <sup>-1</sup> for patients of age over 70 years
Roemeling <i>et al.</i> , <sup>37</sup> 2007	Clinical stage T1c; PSA $\leq 15$ ng ml <sup>-1</sup> ; biopsy Gleason score $\leq 7$
Suardi <i>et al.</i> , <sup>14</sup> 2008	Clinical stage T1c; PSA $\leq 4$ ng ml <sup>-1</sup> ; biopsy Gleason score $\leq 6$

Abbreviation: PSA, prostate-specific antigen.

the assumption that all patients within a given risk group are equal, when, in fact, they can be quite dissimilar and may experience disparate outcomes. Furthermore, the risk estimations derived from such heterogeneous populations are average values that may not apply to the individual patient. A man newly diagnosed with prostate cancer and attempting to decide upon a management strategy presumably cares about his individual prognosis and not about the outcome of a group of men who may not even be representative of his specific clinical situation.

Moreover, the method of counting risk factors assumes, often incorrectly, that each variable exerts equal prognostic weight on the outcome. For example, high Gleason grade has been shown to reflect a poor prognosis irrespective of other clinical or pathologic criteria.<sup>15</sup> Lastly, risk-grouping requires converting continuous variables (e.g., PSA) into categorical variables, which blunts their prognostic value and lowers the overall accuracy of the model.<sup>16</sup>

### IS THERE A BETTER ALTERNATIVE TO RISK GROUPINGS?

To generate more accurate predictions of clinically insignificant disease, more powerful models are needed that incorporate patient-specific variables and generate risk estimates tailored to the individual man. As such, investigators have turned to the development of continuous multivariable prediction models, such as nomograms. Based upon robust multiple regression equations, nomograms are able to analyze multiple variables simultaneously, allowing a greater number of predictors to be considered than would be possible with human calculation. Models with more prognostic factors are more likely to reflect the complexity of a disease like prostate cancer and, therefore, predict outcomes more accurately. Moreover, continuous variables can be kept continuous in a nomogram, whereas risk groupings require creation of cutpoints that are often arbitrary with little prognostic basis. Because of these advantages, nomograms tend to predict outcomes more accurately than other methods of risk estimation, including risk groupings.<sup>17–24</sup>

There are a number of published nomograms based on pre-treatment data that predict clinical end points related to the aggressiveness of prostate cancer and which may be useful in determining eligibility for surveillance (Table 2). Kattan and colleagues<sup>25</sup> developed a nomogram to predict the probability of indolent prostate cancer, defined as a tumor volume <0.5 cc, pathological Gleason score ≤ 6 and confined to the prostate (Figure 1). The nomogram was constructed from a

cohort of 409 patients with low-risk prostate cancer (pretreatment PSA <20, clinical stage T1–T2a, no primary or secondary Gleason grade 4 or 5 cancer in biopsy, <50% positive cores, <20 mm total cancer in biopsy cores). The predictive factors in the model included PSA, clinical stage, primary and secondary biopsy Gleason grade, prostate volume by ultrasound, length of cancer and length of non-cancer in biopsy cores. With internal validation, the full model achieved a concordance index of 0.79. The accuracy of the model was comparable, demonstrating a concordance index of 0.77, when applied to a cohort of 296 low-risk patients treated by radical prostatectomy at the Cleveland Clinic between 1999 and 2007.<sup>26</sup>

Another nomogram predicting indolent disease (defined as organ-confined cancer with tumor volume <0.5 cc and without Gleason 4 or 5 patterns) was developed by Chun *et al.*<sup>27</sup> on a German cohort of 1132 men with biopsy-proven organ-confined prostate cancer who were treated with radical prostatectomy. Predictors consisted of PSA, clinical stage, biopsy Gleason sum, core cancer length and percentage of positive biopsy cores. The model demonstrated an accuracy of 90% in predicting clinically insignificant cancer.

Life expectancy is also a relevant factor to consider when trying to define clinically insignificant disease as up to half of men over the age of 60 years who are diagnosed with prostate cancer will not die of their disease.<sup>4</sup> As such, a tumor that is potentially lethal in a younger man with a substantial life expectancy (e.g., >10–15 years) may not be biologically relevant in an older male with a life expectancy <10 years. To this end, Kattan *et al.*<sup>28</sup> developed a nomogram to predict prostate cancer-specific survival at 10 years among men who did not receive any definitive local therapy (Figure 2). The study cohort consisted of 1911 patients identified from six cancer registries in England between 1990 and 1996 who did not receive any form of local therapy within 6 months of diagnosis. The model was based on PSA, biopsy Gleason score (centrally reviewed), clinical stage, method of diagnosis (biopsy vs. transurethral resection of the prostate), percentage of cancer, age, and the use of androgen deprivation therapy within 6 months of diagnosis. The accuracy of the model was demonstrated to be 0.73.

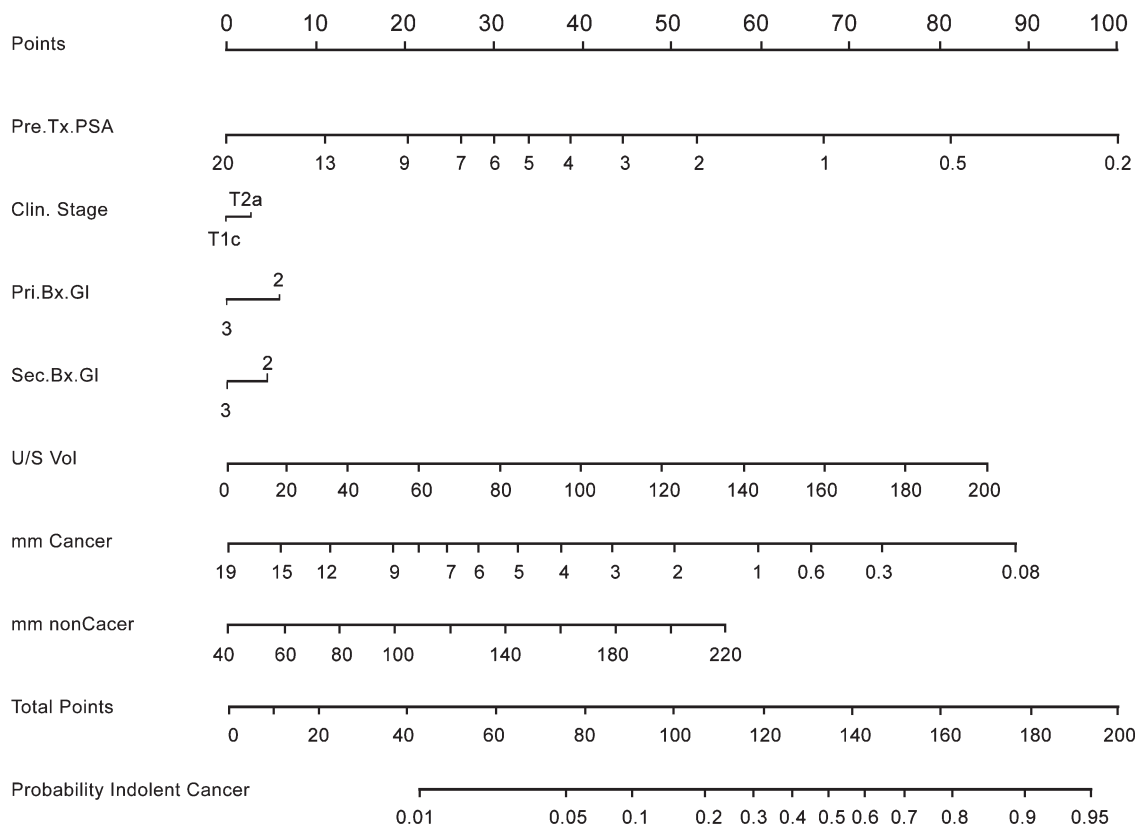
### LIMITATIONS OF NOMOGRAMS

Nomograms are superior to classical risk groupings in the prediction of clinically insignificant cancer, but there are limitations that must be considered when using their risk estimates in patient counseling and decision-making. Most importantly, it should be pointed out that no

**Table 2** Pre-treatment nomograms relevant to the prediction of clinically significant prostate cancer

Nomogram	Outcome predicted	95% CI	Variables
Koh <i>et al.</i> , <sup>38</sup> 2003	Probability of seminal vesicle invasion	0.88	PSA, clinical stage, Gleason grade, % cancer at base
Cagiannos <i>et al.</i> , <sup>39</sup> 2003	Probability of LN involvement	0.76	Clinical stage, Gleason sum and PSA
Kattan <i>et al.</i> , <sup>25</sup> 2003	Probability of indolent cancer	0.79	Serum PSA, clinical stage, biopsy Gleason grade, TRUS volume, % of biopsy cores involved with cancer and high-grade cancer, total length of biopsy cores involved
Ohuri <i>et al.</i> , <sup>40</sup> 2004	Probability of ECE	0.81	Pretreatment PSA, clinical stage, biopsy Gleason sum, % positive cores, % cancer in cores
Chun <i>et al.</i> , <sup>41</sup> 2006	probability of Gleason score upgrading at RP	0.8	PSA, clinical stage, primary and secondary Gleason patterns
Wang <i>et al.</i> , <sup>42</sup> 2006	organ confined cancer	NR	PSA, biopsy Gleason grade, clinical stage, MRI findings
Briganti <i>et al.</i> , <sup>43</sup> 2008	Probability of LN involvement	0.81	PSA, clinical stage, Gleason sum
Chun <i>et al.</i> , <sup>27</sup> 2008	Probability of indolent cancer	0.81–0.90	PSA, clinical stage, biopsy Gleason sum, core cancer length and percentage of positive biopsy cores
Kattan <i>et al.</i> , <sup>44</sup> 2008	Probability of 10-year life expectancy for men not treated with curative intent	0.73	PSA, biopsy Gleason score, clinical stage, method of diagnosis (biopsy vs. TURP), % of cancer, age and use of ADT within 6 months of diagnosis

Abbreviations: ADT, androgen deprivation therapy; CI, concordance index; ECE, extracapsular extension; LN, lymph node; RT, radiation therapy; MRI, magnetic resonance imaging; NR, not reported; PSA, prostate-specific antigen; RP, radical prostatectomy; TRUS, transrectal ultrasound; TURP, transurethral resection of the prostate.



**Instructions for Physician:** Locate the patient’s PSA on the Pre.Tx.PSA axis. Draw a line straight upwards to the Points axis on determine how many points towards having an indolent cancer the patient receives for his PSA. Repeat this process for the remaining axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to find the patient’s probability of having indolent cancer.

**Instruction to Patient:** “Mr. X, if we had 100 men exactly like you, we would expect “predicted probability from nomogram × 100” to have indolent cancer.”

**Figure 1** Nomogram predicting the presence of indolent prostate cancer (pathological Gleason score  $\leq 3+3$ , cancer volume  $<0.5$  ml, organ-confined) based on pretreatment PSA level (Pre.Tx.PSA), clinical stage (Clin.Stage), primary (Pri.Bx.GI) and secondary (Sec.Bx.GI) biopsy, Gleason grade, prostate volume by ultrasound (U/S Vol), length of cancer (mm) in biopsy specimens (mm Cancer) and length of non-cancer (mm) in biopsy specimens (mm nonCancer). PSA, prostate-specific antigen.

nomogram predicts with perfect accuracy. Currently available models can misclassify patients as having insignificant cancer in up to 20% of cases, potentially leading to improper treatment assignment and poor outcomes. However, there are no data demonstrating that the use of nomograms in urological practice have actually had any measurable impact (positive or negative) on prostate cancer outcomes.

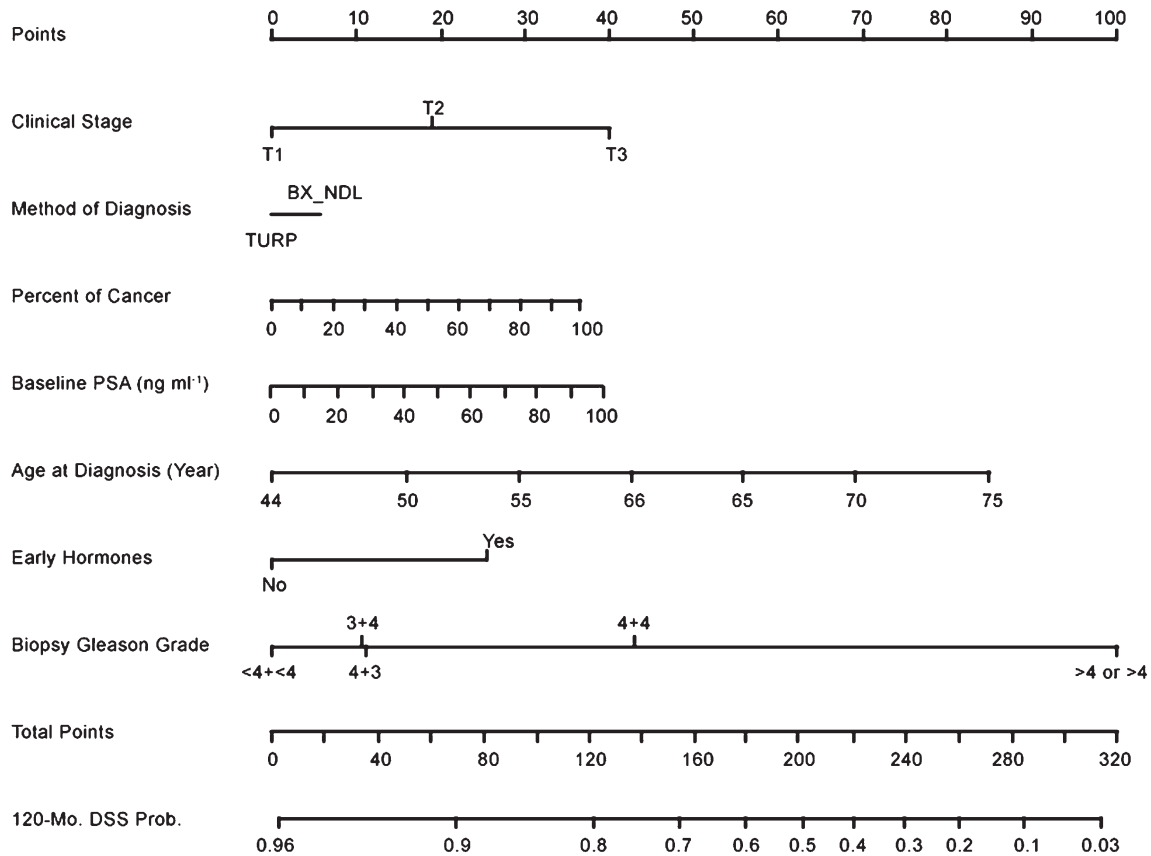
Another question regarding the utility of nomograms in predicting insignificant disease is whether they are applicable to all men newly diagnosed with prostate cancer. Most nomograms are constructed and validated using patients treated at single academic centers, whose demographics and outcomes may be very different from those of patients treated at community hospitals. Even among academic centers, there can be institutional disparities in the quality and availability of medical care as well as non-uniformity in the way in which data are collected and interpreted. Moreover, such disparities make it difficult to compare the relative accuracy of rival nomograms not constructed on a neutral data set, i.e., not compared in a head to head analysis.<sup>29</sup> As such, the concordance indices listed in **Table 2** for the different nomograms are for reference only and are not meant to be used for comparative purposes.

Considering all of these potential limitations, predictions generated by risk groupings or nomograms should not be the sole factor in

determining the probability of insignificant prostate cancer and eligibility for active surveillance. Such a critical decision may indeed benefit from the risk estimates provided by prediction models, but also should be based upon published data, physician judgment and experience, as well as patient preference.

**FUTURE DIRECTIONS**

No currently available prediction model, either risk grouping or nomogram, predicts clinically significant prostate cancer with perfect accuracy. The available data do suggest, however, that nomograms are superior to risk groupings. As such, there is a need to continuously improve and validate current nomograms as well as develop new models. Knowledge of the criteria that determine the quality and utility of a nomogram can provide direction for improvement. The quality of a nomogram is dependent not only upon its predictive accuracy but also on the methods utilized to construct the model. Ideally, the patient cohort on which the nomogram was constructed should be representative of the general population of patients to whom the model will be applied. The nomogram should be based on a sufficient number of cases that also include a large proportion that reach the end point of interest. The nomograms described in this chapter



**Figure 2** Nomogram for predicting 10-year disease-specific survival for men with localized prostate cancer who are initially managed with a deferred treatment strategy. The parameters included in the nomogram are clinical stage, method of diagnosis (needle biopsy (BX\_NDL) vs. transurethral resection of the prostate (TURP)), percentage of cancer in the biopsy specimen, PSA level at diagnosis, age at diagnosis, the use of early androgen deprivation therapy (within 6 months of diagnosis) and biopsy Gleason score. 120-Mo DSS Prob., 120 months disease-specific survival probability. PSA, prostate-specific antigen.

were generally based on single-institution cohorts with potentially skewed demographics and, if not already performed, should be subjected to external validation using large patient cohorts from other institutions. This can adjust for bias due to small sample size of the internal dataset as well as that due to regional differences in patient demographics.

Identification and incorporation of additional predictive markers can improve the accuracy of existing nomograms. Novel molecular and genetic markers, such as PCA3 or the TMPRSS2:ERG gene fusion, may have utility in identifying cases of prostate cancer with favorable prognosis.<sup>30–32</sup> A useful nomogram should also incorporate clinical factors that are reliable, routinely employed in the clinical setting, and easy to obtain. A nomogram that utilizes parameters that require specialized or expensive assays or cumbersome procedures may be impractical for general use.

## CONCLUSIONS

Current evidence suggests that PSA-based screening for prostate cancer is a double-edged sword. PSA testing has undoubtedly improved the early detection of prostate cancer, leading to more men being diagnosed and treated for prostate cancer. However, this has not been translated into a definitive survival or mortality benefit for men with screen-detected cancer and may actually cause harm. The increased incidence of prostate cancer includes a large number of indolent tumors that do not pose a significant health threat and do not require treatment.

Due to the lack of ideal datasets and the difficulty in measuring relevant end points related to lethal prostate cancer, we currently

depend upon prediction models, including risk grouping schema and nomograms, to predict the likelihood of clinically insignificant disease. These models have demonstrated high accuracies in the identification of organ-confined disease. However, organ-confinement does not necessarily preclude the possibility of cancer progression in patients not treated with curative intent. Furthermore, current prediction models are still associated with a 10%–20% rate of misclassification, and their use does not completely exclude the presence of adverse pathologic features at the time of diagnosis. The need to improve and validate current models as well as develop more accurate ones will hopefully form the basis for future research efforts in prostate cancer prediction.

Although imperfect, prediction models currently offer the best estimates of the likelihood of having clinically insignificant prostate cancer. Combined with clinician expertise and patient preference, these risk estimates can form the basis of truly informed decisions regarding the need for immediate intervention versus active surveillance, potentially mitigating some of the problems associated with the contemporary overdiagnosis and overtreatment of prostate cancer.

## COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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