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Predictive and Prognostic Models in Radical Prostatectomy Candidates: A Critical Analysis of the Literature

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Abstract

Context—Numerous predictive and prognostic tools have recently been developed for risk stratification of prostate cancer (PCa) patients who are candidates for or have been treated with radical prostatectomy (RP).

Objective—To critically review the currently available predictive and prognostic tools for RP patients and to describe the criteria that should be applied in selecting the most accurate and appropriate tool for a given clinical scenario.

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Evidence acquisition—A review of the literature was performed using the Medline, Scopus, and Web of Science databases. Relevant reports published between 1996 and January 2010 identified using the keywords *prostate cancer*, *radical prostatectomy*, *predictive tools*, *predictive models*, and *nomograms* were critically reviewed and summarised.

Evidence synthesis—We identified 16 predictive and 22 prognostic validated tools that address a variety of end points related to RP. The majority of tools are prediction models, while a few consist of risk-stratification schemes. Regardless of their format, the tools can be distinguished as *preoperative* or *postoperative*. Preoperative tools focus on either predicting pathologic tumour characteristics or assessing the probability of biochemical recurrence (BCR) after RP. Postoperative tools focus on cancer control outcomes (BCR, metastatic progression, PCa-specific mortality [PCSM], overall mortality). Finally, a novel category of tools focuses on functional outcomes. Prediction tools have shown better performance in outcome prediction than the opinions of expert clinicians. The use of these tools in clinical decision-making provides more accurate and highly reproducible estimates of the outcome of interest. Efforts are still needed to improve the available tools' accuracy and to provide more evidence to further justify their routine use in clinical practice. In addition, prediction tools should be externally validated in independent cohorts before they are applied to different patient populations.

Conclusions—Predictive and prognostic tools represent valuable aids that are meant to consistently and accurately provide most evidence-based estimates of the end points of interest. More accurate, flexible, and easily accessible tools are needed to simplify the practical task of prediction.

Keywords

Prostate cancer; Radical prostatectomy; Prediction tools; Nomograms

1. Introduction

Prostate cancer (PCa) is the most common solid malignancy in men, with 192 280 new cases having been diagnosed in 2009 in the United States [1]. Different treatment options are currently available for men with localised PCa, such as external-beam radiation therapy (EBRT), brachytherapy, and active surveillance. Radical prostatectomy (RP) represents one of the most commonly used therapies for clinically localised PCa. The selection of a candidate for RP remains complex because of the variety of strategies that can be followed in planning the surgical technique, postoperative treatment, and follow-up. Tools that could facilitate the decision-making process in these phases would be very valuable.

In this manuscript, we provide an overview of the currently available predictive (ie, predicting the probability of an outcome without considering the effect of time) and prognostic (ie, predicting the probability of an outcome over time) tools for candidates to RP and for patients who have already undergone the procedure. In addition, we provide objective characteristics that support the use of some models over others. Finally, because several patients with localised PCa may elect other treatment options, we provide a brief summary of prediction tools in patients treated with EBRT or brachytherapy.

2. Evidence acquisition

A review of the literature using the Medline, Scopus, and Web of Science databases was conducted to identify original articles, review articles, and editorials regarding predictive and prognostic tools in patients treated with RP and in candidates for RP. Searches were limited to the English language. The literature search was performed by combining the following terms: *prostate cancer*, *radical prostatectomy*, *predictive tools*, *predictive models*, and *nomograms*. A total of 415 records were retrieved from Medline, 748 from Scopus, and 712 from Web of Science. Subsequently, the search results were pooled, and articles published between 1996 and January 2010 were identified. The articles with the highest level of evidence were selected, reviewed, and summarised, with the consensus of all of the authors of this paper.

3. Evidence synthesis

3.1. Different methods used for clinical decision making

Clinical decision-making may be based on physician experience; randomised, controlled trials (RCTs); or on the information received from decision aids. Experience alone results in poorly reproducible predictions and in excessive interrater variability [2–4]. Moreover, RCTs are too infrequently performed in the context of RP; even when RCT data exist, they are not universally implemented for a number of reasons [5,6]. Therefore, most clinical questions that pertain to PCa cannot be solved using RCT data. As a consequence, several predictive and prognostic tools have been developed to assist with uncertainties related to clinical decision-making. These tools are intended to provide more accurate and highly reproducible estimates of the outcome of interest [7,8]. To date, these tools have shown better performance in outcome prediction than the opinions of expert clinicians in both prostate and breast cancer [9–11].

3.2. How should a model be evaluated?

Predictive tools can be subdivided into risk groupings, look-up tables, classification and regression tree analyses, artificial neural networks, and prediction models, with the latter often presented graphically in the form of a nomogram. Despite their methodologic differences, these models can be compared using several common parameters: discrimination, calibration, generalisability, level of complexity, and clinical net benefit [12–15].

Discrimination and calibration represent the key properties that should invariably be reported when any model is validated. *Discrimination* represents the probability that the tool will correctly predict a poorer outcome for the patient who initially develops the outcome of interest out of a randomly selected pair of patients. Discrimination is usually quantified using the area under curve for binary outcomes and the concordance index for censored data. Both metrics range from 50% (no discrimination) to 100% (perfect discrimination) [12–14,16]. Overall discrimination needs to be complemented with *calibration*, which is an evaluation of the relationship between predicted probabilities and observed rates of the outcome of interest, throughout the entire range of predictions [12–14,16]. Inclusion of

calibration properties is necessary, because a model may predict perfectly well in low-risk patients, but its predictions may be of dismal quality in high-risk individuals.

In addition, discrimination and calibration findings need to be generalisable and applicable to the population of interest. For example, data confirming the validity of a tool in Caucasian patients may not be generalisable to African American patients, even if all other variables are held constant [17]. Therefore, external validation of a predictive or prognostic tool should be mandatory to establish whether the tool works satisfactorily in different patient populations [12,18,19]. Moreover, predictive and prognostic tools need to be simple enough to ensure that physicians are capable of using them in a busy clinical practice.

Finally, a recommended tool should be better than competing tools. Recently, Vickers et al described decision curve analysis, which is used to evaluate the effect of different models on medical decision-making [15]. Decision curve analysis provides a common denominator for comparing predictive tools, as it factors the harms and benefits of a given tool within a single metric, and should therefore complement discrimination and calibration results when different predictive or prognostic tools are compared [15]. Moreover, decision curve analysis is easier to implement than classic decision analysis [20].

3.3. End points of model application in the context of radical prostatectomy

3.3.1. Surgical planning

3.3.1.1. Preoperative prediction of Gleason score upgrading: Gleason score upgrading (GSU) between prostatic biopsy and RP pathology may affect treatment planning (Table 1). Therefore, knowing the probability of GSU may help select the best treatment option according to preoperative characteristics. This is especially important in patients with low-risk PCa who seek less invasive therapy, such as active surveillance, because the presence of potentially life-threatening disease may be underestimated. Five tools can predict the probability of GSU. D'Amico et al ($n = 693$; original discrimination not reported) developed a look-up table based on serum prostate-specific antigen (PSA), clinical stage, and prostate volume for predicting GSU [21]. The last model showed low discrimination (52.3%) at external validation [22]. Chun et al ($n = 2892$; internal discrimination: 80.4%), Kulkarni et al ($n = 175$; internal discrimination: 71.0%), Capitanio et al ($n = 301$; internal discrimination: 66.1%), and Moussa et al ($n = 1017$; internal discrimination: 68.0%) devised four nomograms for predicting GSU that include primary and secondary Gleason score along with several other preoperative variables [22–25]. Of these, both the Kulkarni et al and the Capitanio et al nomograms focused on prediction of GSU in low-risk patients (Gleason score ≤ 6) [23,24]. To date, only the Chun et al nomogram has been externally validated in a European and in a Japanese cohort, showing good discrimination (external discrimination: 74.9% and 79.2%, respectively) [26,27]. However, calibration properties of this nomogram were suboptimal in the Japanese patients [27]. Accordingly, this tool should be given priority in European patients. Other tools are still needed for predicting GSU in other patient populations.

Only one tool for GSU prediction has been externally validated. However, the currently available GSU predictive tools were devised on a sextant prostate biopsy population.

Therefore, these tools need to be validated and/or updated in a contemporary extended prostate biopsy population.

3.3.1.2. Preoperative prediction of life expectancy: Ten years is usually considered the minimum life expectancy prerequisite for RP candidates (Table 2). Unfortunately, clinicians are poor raters of life expectancy [11,28]. Therefore, tools that can accurately identify those individuals who do not have sufficient life expectancy to warrant definitive PCa treatment are needed to help optimise treatment decision-making.

Two models with proven external validity can provide life expectancy estimates. The Tewari et al model for prediction of life expectancy in RP candidates ($n = 1611$; internal discrimination: 71.0%) relies on four variables (patient age, Charlson Comorbidity Index [CCI], biopsy Gleason score, and PSA) to predict 10-yr overall (OS) survival [29]. Conversely, the Walz et al model ($n = 5965$; internal discrimination: 84.0%) relies solely on age and baseline comorbidities to predict life expectancy in RP candidates [30]. In external validation, both models showed excellent discrimination: 81.0% and 82.0% for the Tewari et al model and the Walz et al model, respectively [30,31]. To date, only the Walz et al nomogram was externally validated in both an American and a European cohort. Therefore, this model should be chosen over the Tewari et al model when life expectancy predictions are made in European patients. Two competing models showed lower discrimination (from 71.0% to 73.0%) and should represent second choices when life expectancy predictions are required [32,33].

3.3.1.3. Preoperative prediction of pathologic stage: Prediction of pathologic stage is obviously important in surgical treatment planning (Table 1). Patients with a low probability of having PCa with extracapsular extension (ECE) of their disease may benefit from a more conservative (eg, nerve-sparing) surgery relative to individuals with a high risk of ECE. Similarly, individuals at high risk of having seminal vesical invasion (SVI) or lymph node invasion (LNI) may benefit from more extensive surgical approaches as well as from the prompted use of adjuvant therapies.

Partin et al ($n = 4133$; internal discrimination: 72.4%) pioneered an evidence-based approach for the prediction of pathologic stage at RP. The Partin tables predict the probability of ECE, SVI, and LNI after RP according to the patient's PSA level, clinical stage, and biopsy Gleason sum [34]. This tool has been subjected to numerous updates and external validations [17,35–39]. Some of them failed to confirm the ability of the Partin tables to generate accurate and/or well-calibrated predictions [38–40]. This was particularly evident in European patients, where the Partin tables showed significant departures from ideal predictions for each of the three predicted outcomes [39,40]. Conversely, a recent external validation in the Surveillance, Epidemiology and End Results dataset showed good discrimination for both SVI (74%) and LNI (77%) predictions [17]. However, calibration results were not reported [17].

Lack of ability to provide side-specific ECE predictions represents a limitation of the Partin tables. This information is particularly important during surgical planning, because the decision to preserve one or both neurovascular bundles affects functional outcomes and,

subsequently, the patient's quality of life. The issue of side-specific ECE predictions was addressed by two nomograms devised by Ohori et al ($n = 763$; internal discrimination: 80.6%) and by Steuber et al ($n = 1118$; internal discrimination: 84.0%). Both nomograms rely on serum PSA, clinical stage, biopsy Gleason sum, percent of positive cores, and percent of cancer in positive cores [41,42]. To date, only the Steuber et al nomogram has been externally validated (89.0%) [43].

Koh et al ($n = 763$), Baccala et al ($n = 6740$), and Gallina et al ($n = 666$) developed three preoperative nomograms for SVI prediction that showed internal discrimination ranging from 78% to 88% [44–46]. All these nomograms include serum PSA, clinical stage, and biopsy Gleason sum among the predictors of SVI. Of those, only the Gallina et al nomogram was externally validated in a cohort of 2584 patients who underwent a robot-assisted laparoscopic radical prostatectomy (RARP) and showed 81.0% discrimination [47].

Cagiannos et al ($n = 5510$; internal discrimination: 78.0%) developed a nomogram for prediction of LNI at RP according to preoperative PSA, clinical stage, and biopsy Gleason sum [48]. Using the same variables, Briganti et al devised two nomograms to predict LNI when extended pelvic lymph node dissection (PLND) was performed ($n = 602$; internal discrimination 76.0%) and LNI outside the obturator fossa ($n = 565$; internal discrimination: 80.2%) [49,50]. The former nomogram was externally validated in a European cohort and showed 82.1% discrimination [51]. However, this external validation was performed in patients treated with limited PLND, thus potentially underestimating the real LNI rate [49]. A formal external validation of this nomogram in patients treated with extended PLND is needed.

In sum, several tools are available for the prediction of pathologic stage (ECE, SVI, and LNI) at RP. Of those, some have been externally validated and should be given higher priority when making pathologic stage predictions. However, it is worth noting that most external validations were performed in a single cohort [43,47,51].

3.3.1.4. Preoperative prediction of perioperative mortality: Perioperative mortality remains an important issue in any type of surgery (Table 2). Mortality rates after RP can vary from 0.1% to 0.5% according to the type of population and type of institution [52,53]. Recently, Walz et al ($n = 9208$) devised a model predicting 30-d mortality after RP and showed that age, comorbidities, and surgical expertise are capable of predicting perioperative mortality with 72.3% discrimination [54]. This model still awaits external validation.

3.3.1.5. Preoperative prediction of biochemical recurrence: Biochemical recurrence (BCR) is widely used as an end point to assess RP efficacy (Table 3). BCR also represents a marker of metastatic progression and PCa-specific mortality [55,56]. Despite the widespread use of BCR, uniform criteria to define BCR after RP are lacking, and numerous definitions are used in the medical literature, leading to different results in outcome reporting [57]. Of note, estimates of risk ratio and predictive accuracy are generally robust regarding the definition of BCR [58]. Stratifying patients according to their risk of BCR may be useful in

selecting those who may benefit from an adjuvant therapy on the basis of their likelihood of treatment failure.

Preoperative prediction of BCR can be accomplished with the D'Amico et al risk stratification scheme ($n = 888$; original discrimination not reported) [59], the Stephenson et al nomogram ($n = 1978$; internal discrimination: 76.0%) [60], and the Cancer of the Prostate Risk Assessment (CAPRA) score ($n = 1439$; internal discrimination: 66.0%) [61]. All of these models rely on commonly available variables, such as PSA, clinical stage, and biopsy Gleason sum, and all have been externally validated. Accordingly, their use should be encouraged [62–66]. It is noteworthy that both the Stephenson nomogram and the CAPRA score showed better discrimination abilities than the D'Amico et al risk stratification scheme [62–66]. Therefore, when preoperative BCR predictions are made, these two models should be prioritised over the D'Amico et al risk stratification scheme. However, further comparative studies between the Stephenson nomogram and the CAPRA score are still needed to determine whether one model should be chosen over the other.

3.3.1.6. Preoperative prediction of prostate cancer-specific mortality: PCa-specific mortality (PCSM) represents the most important cancer-control end point in RP candidates (Table 2). D'Amico et al ($n = 4946$; original discrimination not reported) and Cooperberg et al ($n = 5378$; internal discrimination: 80.0%) devised two risk-stratification schemes to predict PCSM [67,68]. Both models rely on preoperative patient and tumour characteristics, such as age, biopsy Gleason sum, serum PSA level, and clinical stage [67,68]. Unfortunately, the discrimination and calibration of these models have not been externally validated.

More recently, Stephenson et al devised a competing-risks regression-based nomogram for predicting PCSM in the PSA era ($n = 6398$) [69]. This nomogram, which is based on biopsy Gleason grade, serum PSA, and clinical stage, was externally validated in an external cohort of 6278 patients, showing an 82.0% discrimination [69]. Therefore, when predicting PCSM, the prognostic model developed by Stephenson et al should be chosen over the two other tools.

3.3.1.7. Preoperative prediction of functional outcomes: Similarly to cancer-control outcomes, functional outcomes can be predicted prior to RP, thus helping clinicians choose the best treatment options according to preoperative patient and tumour characteristics (Table 1). Eastham et al ($n = 1577$; internal discrimination: 77.3%) developed a nomogram that predicts cancer control outcomes (BCR-free survival) combined with continence and potency after RP (trifecta probability) according to various preoperative characteristics (PSA, clinical stage, biopsy Gleason core, pretreatment erectile function, months from RP, and age at RP) [70]. Recently, Briganti et al developed a preoperative risk stratification tool ($n = 435$; internal discrimination: 69.1%) aimed at predicting erectile function recovery after bilateral nerve-sparing radical retropubic prostatectomy [71]. This tool relies on patient age, CCI, and preoperative International Index of Erectile Function questionnaire results and has been externally validated in a European cohort of patients treated with RARP [72]. However, its external discrimination has not been quantified [72]. Despite good

discrimination, because all patients were operated on by high-volume surgeons, the applicability of these models may be limited to the tertiary care setting.

3.3.2. Immediate postoperative counselling

3.3.2.1. Postoperative prediction of biochemical recurrence: Prediction of BCR after RP represented the focus of several previously reported prognostic tools (Table 3) [73–76]. Early BCR prediction was first addressed by D'Amico et al ($n = 862$; original discrimination not reported), who devised a look-up table based on serum PSA, pathologic stage, Gleason sum, and surgical margin status for 2-yr BCR predictions [73]. Unfortunately, this model was never externally validated. Since then, Walz et al has devised ($n = 2911$) and externally validated ($n = 2825$; external discrimination: 82.0%) a highly accurate tool for prediction of BCR 2 yr after RP [74]. This model, which relies on serum PSA, pathologic Gleason sum, surgical margin status, ECE, SVI, and LNI, can be used to discriminate among individuals who require adjuvant EBRT and those who can be observed [74].

BCR up to 10 yr after RP can be predicted using the postoperative Stephenson nomogram ($n = 1881$; internal discrimination: 86.0%), which relies on the same variables included in the Walz et al early BCR prediction nomogram [75]. A new, important feature of the Stephenson et al nomogram is the possibility of adjusting predictions according to disease-free interval. This tool has been externally validated in two other North American cohorts ($n = 1782$ and $n = 1357$) with highly satisfactory results (discrimination: 79.0–81.0%) [75].

BCR can also be predicted for even more distant end points (up to 20 yr after RP) using the nomogram developed by Suardi et al [76]. This nomogram relies on pathologic Gleason sum, pathologic stage, surgical margin status, type of surgery, and adjuvant radiation therapy (RT), and it has been externally validated in a European cohort (discrimination: 77.9–86.3%). Moreover, its predictions can be adjusted according to the disease-free interval [76].

In sum, three externally validated nomograms are available for BCR predictions. Of these, the Stephenson et al nomogram has the greatest flexibility in providing BCR predictions at different time points (1–10 yr after RP) [75]. The Walz et al nomogram is most specific for early BCR predictions [74]. Finally, the Suardi et al nomogram is best suited to predictions beyond 10 yr and illustrates the persistent risk of BCR despite 10 yr of follow-up [76].

3.3.3. Long-term end points

3.3.3.1. Prediction of progression to metastatic disease: After RP, patients may develop BCR, and a portion of those patients may eventually develop bone metastases (Table 4). Three investigators devised tools capable of predicting the probability of metastatic progression after BCR. Pound et al examined 1997 RP patients (original discrimination not reported) and found that PSA doubling time (PDT) <10 mo, time to BCR 2 yr, and pathologic Gleason score 8–10 were the strongest predictors of bone metastasis and stratified the 3-, 5-, and 7-yr probability of such metastases according to these three values [55]. Unfortunately, external validation of the tool was not performed. Dotan et al ($n = 239$; internal discrimination: 93.0%) and Slovin et al ($n = 148$; internal discrimination: 69%)

combined PSA kinetics, along with other patient characteristics, to devise two nomograms predicting the probability of radiographically detectable bone metastases after BCR [77,78]. Porter et al ($n = 752$; internal discrimination: 76.0–80.2%) also devised a nomogram for predicting metastatic progression at 5, 10, 15, and 20 yr after RP that can be adjusted according to the disease-free interval [79]. Finally, Cooperberg et al ($n = 5378$; internal discrimination 78.0%) devised a risk stratification scheme (CAPRA score) that also focused on bone metastasis after RP [68]. To date, neither of the models has undergone formal external validation.

In sum, no available tools with externally confirmed discrimination can assist the clinician with the prediction of bone metastasis after RP. As a consequence, the existing models need to be used with caution when determining the timing or type of staging investigations in patients treated with RP.

3.3.3.2. Postoperative prediction of prostate cancer–specific mortality: D’Amico et al ($n = 5918$) and Zhou et al ($n = 498$) observed that the PCSM of patients with localised or locally advanced PCa can be stratified according to PDT (Table 2) [80,81]. Subsequently, Freedland et al ($n = 379$; internal discrimination: 84.0%) devised a look-up table for the prediction of PCSM in patients with an established PSA recurrence after RP [56]. This model relies on postoperative variables—namely, PDT, pathologic Gleason sum, and time from surgery to BCR [56]. Unfortunately, as in the case of several other tools, the Freedland et al model still awaits external validation. Consequently, caution should be taken when using it to stratify the risk of PCSM after RP.

3.4. Models in the context of external-beam radiation therapy or focal therapy

Although RP remains one of the most commonly used therapies, an increasingly higher number of patients with localised PCa are currently managed with different treatment strategies (Table 5). Because no randomised trials directly comparing the efficacy and morbidity of these various treatment approaches have been undertaken, management decisions are often based on physician judgment and patient preferences. Therefore, prediction tools can be used to provide the most unbiased estimates of clinically relevant end points and facilitate patient counselling.

Many of the prediction tools that we previously discussed (eg, tools predicting pathologic stage, Gleason score upgrading, life expectancy) may help patients and clinicians in deciding the most appropriate treatment option. In addition, several other tools have been developed to predict BCR, survival, or progression to distant metastasis in patients treated with EBRT or brachytherapy [59,67,78,81–88]. The currently available tools for these patient categories are summarised in Table 5.

3.5. Limitations of existing models

Although the existing models provide an evidence-based approach to various clinical scenarios in the management of RP patients, several limitations persist. Lack of external validation for several of the existing tools represents the most important limitation, because it may limit the model’s applicability to a population of patients different from that used for

its development [18,19]. Moreover, lack of periodic updates that reflect changes in patient and disease characteristics may undermine the applicability of some models to contemporary patient populations. For example, some of the preoperative nomograms addressing GSU rely on a sextant prostatic biopsy population, which is now considered obsolete [22].

Predictive and prognostic models remain imperfect in their discrimination properties and in their calibration characteristics. Therefore, the use of novel, promising predictive or prognostic variables is required to reduce the error margin of existing models [89,90]. Several biomarkers have demonstrated a powerful ability to improve models' predictions. For example, transforming growth factor- β 1, interleukine-6-soluble receptor, plasminogen activator inhibitor type 1, human glandular kallikrein-2, or gene expression signatures significantly improved the ability of different BCR predictive models to discriminate [91–95]. Shariat et al demonstrated that a panel of blood-based biomarkers improved the preoperative prediction of BCR [96]. Similarly, plasma endoglin improved predictions of LNI at RP [97].

Lack of consideration of competing risks represents another problem with some models, especially those that predict distant end points, such as long-term BCR, metastatic progression, or PCSM. Lack of consideration of competing risks may confound the association between clinical and pathologic predictors and the outcome of interest. Similarly, only a few tools that predict BCR, metastatic progression, or PCSM adjust for disease-free interval since RP [75,76,79]. Adjustment for disease-free interval should be made, and models that allow it may provide more realistic predictions of the outcome of interest.

Besides methodologic issues, clinicians may be unaware of how and when to apply specific predictive or prognostic tools [98]. Recently, Nguyen and Kattan addressed this issue and systematically organised the currently available PCa prediction tools within a metagram, which represents a framework on which existing PCa prediction tools are organised and stratified by their accuracy, quality, and usefulness in a clinical setting [99]. The metagram showed that there is a great need for additional models as well as improvement in the accuracy of existing tools. Moreover, the existing nomograms may not provide adequate flexibility when it comes to predictor variables. For example, clinicians may not dispose of all the variables that were used to devise a specific model. Therefore, improvements in the accessibility and flexibility of predictive and prognostic tools are still needed to further promote their use in everyday clinical practice.

Finally, it deserves mention that predictive models reduce the amount of averaging. Nevertheless, they are based on averages of outcomes in patients with specific baseline risk factors. In addition, to the best of our knowledge, no tools are capable of quantifying the benefit of RP relative to other treatment modalities, such as active surveillance, EBRT, or focal therapy. Although prediction tools may help clinicians in choosing the best treatment option by stratifying the risk of harbouring a specific outcome (eg, Gleason score upgrading or PCa stage), no tools are capable of indicating the optimal therapy. Therefore, clinicians still have to carefully interpret the prediction tool results and discuss the risk–benefit ratio of any treatment type with the patient.

4. Conclusions

A recent international consensus conference on predictive modelling in PCa concluded that “nomograms are here to stay” [100]. Moreover, despite the large number of available tools, additional models are still needed [99]. Recently, Nguyen and Kattan observed that only 31 out of 160 possible treatment–outcome combinations are covered by existing models [99]. However, the applicability of existing tools needs to be improved. Vickers et al suggested that predictive and prognostic models should be grouped into a unique platform to provide for the possibility of handling missing data and changing predictions with changing data or changing status of the patient and to provide better flexibility (ie, the possibility of generating predictions for more than one outcome) [101].

Similarly, the accessibility of the existing tools needs to be simplified. To date, only three Web sites (www.nomogram.org, www.nomograms.org, and www.clinicriskcalculators.org) offer a structured overview and easy access to several nomograms for prediction of numerous outcomes in PCa patients. In the future, personal digital assistant–based nomograms will likely complement Web-based tools and will further increase their accessibility and improve ease of use. Clearly, the optimal solution is for predictive models to be built into electronic medical records so that predictions are automatically generated from a patient’s medical data.

Finally, a partially unanswered question remains as to whether nomograms improve patient outcomes or other indicators of quality of care. To date, no formal trials have addressed this question. However, data indicate that specific questions are answered more accurately if model predictions are used instead of even expert clinicians’ ratings [9–11]. Using decision curve analyses, Vickers et al recently demonstrated that the use of predictive tools resulted in better clinical outcomes both in PCa and bladder cancer [102,103].

Therefore, at least partial evidence supports the benefits of predictive or prognostic models relative to experience-based predictions. Based on this evidence, the last version of the European Association of Urology guidelines for PCa recommends the use of nomograms for predicting Gleason score, pathologic T and N stages, PCSM [104]. Nonetheless, these data are scant, and more extensive proof continues to be required.

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Table 1

Prediction Gleason score upgrading, prediction of pathologic stage, and prediction of functional outcomes in men treated with radical prostatectomy for clinically localised prostate cancer

Reference	Year	Prediction form	Outcome	No. of patients	Variables	Discrimination	Validation	
							Internal	External
Prediction of Gleason score upgrading								
D'Amico et al [21]	1999	Look-up table	Gleason score upgrading (defined as 50% or higher probability of Gleason 4)	693	PSA, clinical stage, prostate volume	Internal: Not reported External: 52.3%	–	X
Chun et al [22]	2006	Nomogram	Gleason score upgrading (defined as any upgrade from prostatic biopsy to RP pathology)	2982	PSA, clinical stage, primary biopsy Gleason, secondary biopsy Gleason	Internal: 80.4% External: 74.9–79.0%	X	X
Kulkarni et al [23]	2007	Nomogram	Gleason score upgrading (defined as upgrade from Gleason sum 6 to Gleason sum 7)	175	Age, PSA, clinical stage, primary biopsy Gleason, secondary biopsy Gleason	Internal: 71.0%	X	–
Capitanio et al [24]	2009	Nomogram	Gleason score upgrading (defined as upgrade from Gleason sum 6 to Gleason sum 7)	301	Biopsy Gleason sum, number of cores, number of positive cores	Internal: 66.1%	X	–
Moussa et al [25]	2009	Nomogram	Gleason score upgrading (defined as upgrade from Gleason sum 6 to Gleason sum 7 and from primary Gleason 3 to primary Gleason 4)	175	Age, race, abnormal DRE, prostate volume, clinical stage, number of previous biopsies, PSA, number of cores, number of positive cores, percent of cancer in positive cores, secondary biopsy Gleason, perineural invasion, inflammation, HGPIN, atypia	Internal: 68.0%	X	–
Prediction of pathologic stage								
Partin et al [34]	1997	Look-up table	Pathologic stage (ECE, SVI, LND)	4133	Biopsy Gleason sum, clinical stage, PSA	Internal: 72.4% External: 71.0–76.0%	X	X
Ohori et al [41]	2004	Nomogram	Side-specific ECE	763	PSA, clinical stage, side-specific biopsy Gleason sum, side-specific percent of positive cores, side-specific percent of cancer in positive cores	Internal: 80.6%	X	–
Steuber et al [42]	2006	Nomogram	Side-specific ECE	1118	PSA, clinical stage, biopsy Gleason sum, percent of positive cores, percent of cancer in positive cores	Internal: 84.0%	X	–
Koh et al [44]	2003	Nomogram	SVI	763	PSA, clinical stage, primary and secondary Gleason sum, percent of cancer at the base	Internal: 88.3%	X	–

Reference	Year	Prediction form	Outcome	No. of patients	Variables	Discrimination	Validation	
							Internal	External
Baccala et al [45]	2007	Nomogram	SVI	6740	Age, PSA, biopsy Gleason sum, clinical stage	Internal: 80.0%	X	-
Gallina et al [46]	2007	Nomogram	SVI	666	PSA, clinical stage, biopsy Gleason sum, percent positive biopsy cores	Internal: 79.2% External: 81.0%	X	X
Cagiannos et al [48]	2003	Nomogram	LNI assessed with limited pelvic lymphadenectomy	5510	PSA, clinical stage, biopsy Gleason sum	Internal: 76.0%	X	-
Briganti et al [49]	2006	Nomogram	LNI assessed with extended pelvic lymphadenectomy (10 nodes removed)	602	PSA, clinical stage, biopsy Gleason sum	Internal: 76.0% External: 82.1–82.4%	X	X
Briganti et al [50]	2007	Nomogram	LNI (probability of exclusive non-obturator lymph node metastases)	565	PSA, clinical stage, biopsy Gleason sum	Internal: 80.2%	X	-
Prediction of functional outcomes								
Eastham et al [70]	2008	Nomogram	Trifecta probability (BCR, continence, potency)	1577	PSA, clinical stage, biopsy Gleason core, pretreatment erectile function, months from RP, age at RP	Internal: 77.3 %	X	-
Briganti et al [71]	2010	Probability graph	Erectile function recovery	435	Age, CCI score, baseline IIEF	Internal: 69.1% External: Not reported	X	X

PSA = prostate-specific antigen; RP = radical prostatectomy; DRE = digital rectal examination; HGPIN = high-grade prostatic intraepithelial neoplasia; ECE = extracapsular extension; SVI = seminal vesical invasion; LNI = lymph node invasion; BCR = biochemical recurrence, CCI = Charlson Comorbidity Index; IIEF = International Index of Erectile Function.

Table 2

Prediction of perioperative mortality, prostate cancer-specific mortality, perioperative mortality, and life expectancy in radical prostatectomy candidates

Reference	Yr	Prediction form	Outcome	No. of patients	Variables	Discrimination	Validation	
							Internal	External
Preoperative prediction of perioperative mortality								
Walz et al [54]	2007	Nomogram	30-d mortality after RP	9208	Age, patient comorbidities, and surgical volume	Internal: 67.1%	X	–
Preoperative prediction of PCSM								
D'Amico et al [67]	2003	Probability graph	PCSM	4946	Biopsy Gleason sum, clinical stage, PSA	Not reported	–	–
Cooperberg et al [68]	2009	Probability graph	PCSM (5 and 10 yr after RP)	10627 (5378 RP patients)	Age, PSA, biopsy Gleason sum, clinical stage, percent positive biopsy	Internal: 80.0%	X	–
Stephenson et al [69]	2009	Nomogram	PCSM (10 and 15 yr after BCR)	6398	Primary and secondary Gleason grade, PSA, clinical stage	External: 82.0%	–	X
Postoperative prediction of PCSM								
Zhou et al [81]	2005	Probability graph	PCSM (5 yr after BCR)	498	PDT, biopsy Gleason sum	Not reported	–	–
Freedland et al [56]	2005	Look-up table	PCSM (5, 10, and 15 yr after BCR)	379	PDT, Gleason sum, time from surgery to BCR	Internal: 84.0%	X	–
Preoperative prediction of life expectancy								
Albertsen et al [32]	1996	Probability formula	OS (10 yr)	451	Age, Gleason sum, and index of coexistent disease category	Internal: Not reported External: 71.0%	–	X
Tewari et al [29]	2004	Probability graph	OS (10 yr)	1611	Age, race, comorbidity, PSA, Gleason sum, treatment type	Internal: Not reported External: 70.0% and 81.0%	–	X
Cowen et al [33]	2006	Nomogram	Life expectancy (5, 10, and 15 yr)	506	Age, CCI, presence of angina, systolic blood pressure, BMI, smoking, marital status, PSA< Gleason sum, clinical stage, treatment type	Internal: 73.0%	X	–
Walz et al [30]	2007	Nomogram	Life expectancy (10 yr)	9131 (5955 RP patients)	Age, CCI, treatment type	Internal: 84.3% External: 82.0%	X	X

RP = radical prostatectomy; PCSM = prostate cancer-specific mortality; PSA = prostate-specific antigen; BCR = biochemical recurrence; PDT = PSA doubling time; OS = overall survival; CCI = Charlson Comorbidity Index; BMI = body mass index.

Table 3
Preoperative and postoperative prediction of biochemical recurrence in men treated with radical prostatectomy

Reference	Yr	Prediction form	BCR, yr	No. of patients	Variables	Discrimination	Validation	
							Internal	External
Preoperative prediction of BCR								
D'Amico et al [59]	1998	Probability graph	3 and 5	888	Biopsy Gleason sum, clinical stage, PSA	Internal: Not reported External: 65.5%	–	X
Cooperberg et al [61]	2005	Probability graph	3 and 5	1439	Age, PSA, biopsy Gleason sum, clinical stage, percent positive biopsy	Internal: 66.0% External: 68.0–81.0%	X	X
Stephenson et al [60]	2006	Nomogram	1–10	1978	PSA, clinical stage, biopsy Gleason sum, yr of surgery, number of positive and negative cores	Internal: 76.0% External: 79.0%	X	X
Postoperative prediction of BCR								
D'Amico et al [73]	1998	Look-up table	2	862	PSA, pathologic stage, Gleason sum, surgical margin status	Not reported	–	–
Walz et al [74]	2009	Nomogram	2	2911	PSA, Gleason sum, surgical margin status, ECE, SVI, LNI	Internal: Not reported External: 82.0%	–	X
Stephenson et al [75]	2005	Nomogram	10	1881	PSA, Gleason sum, ECE, SVI, LNI, surgical margin status	Internal: 86.0% External: 79.0–81.0%	X	X
Suardi et al [76]	2008	Nomogram	5, 10, 15, and 20	601	Gleason sum, pathologic stage, surgical margin status, type of surgery, adjuvant RT	Internal: 77.2–80.6% External: 77.9–86.3%	X	X

BCR = biochemical recurrence; PSA = prostate-specific antigen; ECE = extracapsular extension; SVI = seminal vesical invasion; LNI = lymph node invasion; RT = radiation therapy.

Table 4

Prediction of metastatic progression after radical prostatectomy

Reference	Yr	Prediction form	Patient population	Outcome	No. of Patients	Variables	Discrimination	Validation	
								Internal	External
Progression to metastatic disease									
Pound et al [55]	1999	Regression tree	BCR after RP	Metastasis (metastatic disease-free probability at 3, 5, and 7 yr)	315	PDT, Gleason sum, time to BCR	Not reported	–	–
Dotan et al [77]	2005	Nomogram	BCR after RP	Positive bone scan	239	Pre-treatment PSA, surgical margin status, SVI, Gleason sum, trigger PSA, ECE, PSA slope, PSA velocity	Internal: 93.0%	X	–
Slovin et al [78]	2005	Nomogram	BCR after RP	Metastasis (1 and 2 yr after treatment)	74	Baseline PSA, PDT, pathologic stage, Gleason sum	Internal: 69.0%	X	–
Porter et al [79]	2008	Nomogram	RP	Metastasis (5, 10, 15, and 20 yr after RP)	752	Pathologic stage, Gleason sum, comorbidity, adjuvant RT	Internal: 76.0–82.0%	X	–
Cooperberg et al [68]	2009	Probability graph	RP	Metastasis (5 and 10 yr after RP)	10 627 (5378 RP patients)	Age, PSA, biopsy Gleason sum, clinical stage, percent positive biopsy	Internal: 78.0%	X	–

BCR = biochemical recurrence; RP = radical prostatectomy; PDT = PSA doubling time; PSA = prostate-specific antigen; SVI = seminal vesical invasion; ECE = extracapsular extension; RT = radiation therapy.

Table 5

Predictions of biochemical recurrence, survival, or progression to distant metastasis in patients treated with external-beam radiation therapy or brachytherapy

Reference	Yr	Prediction form	Patient population	BCR, yr	No. of patients	Variables	Discrimination	Validation	
								Internal	External
Prediction of BCR									
Pisansky et al [82]	1997	Probability graph	EBRT	5	500	Biopsy Gleason sum, clinical stage, PSA	Not available	–	–
D'Amico et al [59]	1998	Probability graph	EBRT and brachytherapy	3, 5	766 and 218	Biopsy Gleason sum, clinical stage, PSA	Not available	–	–
Kattan et al [83]	2000	Nomogram	EBRT	5	1042	PSA, biopsy Gleason sum, clinical stage, neoadjuvant ADT, radiation dose delivered	Internal: 73% External: 76%	X	X
Kattan et al [84]	2001	Nomogram	Brachytherapy	5	920	Biopsy Gleason sum, clinical stage, PSA, co-administration of EBRT	Internal: Not reported External: 61–64%	–	X
Zelevsky et al [86]	2007	Nomogram	EBRT	5, 10	2253	PSA, biopsy Gleason sum, clinical stage, neoadjuvant ADT, radiation dose delivered	Internal: 72%	X	–
Potters et al [87]	2010	Nomogram	Brachytherapy	9	5931	Clinical stage, biopsy Gleason sum, isotope, EBRT, minimum dose to 90% of the prostate, PSA	Internal: 71%	X	–
Prediction of survival/progression to distant metastasis									
Reference	Yr	Prediction form	Patient population	Outcome	No. of patients	Variables	Discrimination	Internal	External
D'Amico et al [88]	2002	Probability graph	EBRT	PCSM (10 yr)	381	Biopsy Gleason sum, clinical stage, PSA	Not available	–	–
D'Amico et al [67]	2003	Probability graph	EBRT	PCSM (8 yr)	2370	Biopsy Gleason sum, clinical stage, PSA	Not available	–	–
Zhou et al [81]	2005	Probability graph	EBRT	PCSM (5 yr)	661	PDT, biopsy Gleason sum	Not available	–	–
Kattan et al [85]	2003	Probability nomogram development	EBRT	Progression to metastasis (5 yr)	1677	PSA, clinical stage, biopsy Gleason sum	Internal: Not reported External: 81%	X	X
Slovin et al [78]	2005	Probability nomogram development	EBRT	Progression to metastasis (1–2 yr)	71	Baseline PSA, PDT, pathologic T stage, Gleason sum	Internal: 69%	X	–

BCR = biochemical recurrence; EBRT = external-beam radiation therapy; PSA = prostate-specific antigen; ADT = androgen-deprivation therapy; PCSM = prostate cancer specific mortality; PDT = PSA doubling time.