Online version at http://www.minervamedica.it

Minerva Urologica e Nefrologica 2017 December;69(6):556-66
DOI: 10.23736/S0393-2249.17.02832-6

REVIEW

Decision-making tools in prostate cancer: from risk grouping to nomograms

Paolo FONTANELLA [1], Luigi BENECCHI [2], Angelica GRASSO [3], Vipul PATEL [4], David ALBALA [5], Claude ABBOU [6], Francesco PORPIGLIA [7], Marco SANDRI [8], Bernardo ROCCO [3, 9] *, Giampaolo BIANCHI [9]

[1]Department of Surgery, Regional Hospital of Mendrisio, Mendrisio, Switzerland; [2]Department of Urology, Cremona Hospitals, Cremona, Italy; [3]Department of Urology, Ca' Granda Institute for Research and Care, Maggiore Polyclinic Hospital, Milan, Italy; [4]Department of Urology, College of Medicine, Global Robotics Institute, University of Central Florida, Florida Hospital Celebration Health, Kissimmee, FL, USA; [5]Department of Urology, Associated Medical Professionals and Crouse Hospital, Syracuse, NY, USA; [6]Department of Urology, Henri Mondor Hospital, Assistance-Publique Hopitaux de Paris, Créteil, France; [7]Department of Urology, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Turin, Italy; [8]DMS StatLab, Data Methods and Systems Statistical Laboratory, University of Brescia, Brescia, Italy; [9]Department of Urology, University of Modena and Reggio Emilia, Modena, Italy

*Corresponding author: Bernardo Rocco, Department of Urology, University of Modena and Reggio Emilia, Modena Polyclinic, Viale del Pozzo, 41124 Modena, Italy. E-mail: bernardo.rocco@gmail.com

ABSTRACT

INTRODUCTION: Prostate cancer (PCa) is the most common solid neoplasm and the second leading cause of cancer death in men. After the Partin tables were developed, a number of predictive and prognostic tools became available for risk stratification. These tools have allowed the urologist to better characterize this disease and lead to more confident treatment decisions for patients. The purpose of this study is to critically review the decision-making tools currently available to the urologist, from the moment when PCa is first diagnosed until patients experience metastatic progression and death.

EVIDENCE ACQUISITION: A systematic and critical analysis through Medline, EMBASE, Scopus and Web of Science databases was carried out in February 2016 as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The search was conducted using the following key words: "prostate cancer," "prediction tools," "nomograms."

EVIDENCE SYNTHESIS: Seventy-two studies were identified in the literature search. We summarized the results into six sections: Tools for prediction of life expectancy (before treatment), Tools for prediction of pathological stage (before treatment), Tools for prediction of survival and cancer-specific mortality (before/after treatment), Tools for prediction of biochemical recurrence (before/after treatment), Tools for prediction of metastatic progression (after treatment) and in the last section biomarkers and genomics.

CONCLUSIONS: The management of PCa patients requires a tailored approach to deliver a truly personalized treatment. The currently available tools are of great help in helping the urologist in the decision-making process. These tests perform very well in high-grade and low-grade disease, while for intermediate-grade disease further research is needed. Newly discovered markers, genomic tests, and advances in imaging acquisition through mpMRI will help in instilling confidence that the appropriate treatments are being offered to patients with prostate cancer.

(*Cite this article as:* Fontanella P, Benecchi L, Grasso A, Patel V, Albala D, Abbou C, *et al*. Decision-making tools in prostate cancer: from risk grouping to nomograms. Minerva Urol Nefrol 2017;69:556-66. DOI: 10.23736/S0393-2249.17.02832-6)

Key words: Prostate neoplasms - Prostatectomy - Nomograms - Diagnosis.

Introduction

Prostate cancer (PCa) is the most common solid neoplasm and the second leading cause of cancer death in men. In the United States and in Europe, starting with the late 1980's and into the early 1990's, there was a significant increase in diagnosis and treat-

ment of patients with PCa. This spike in diagnosis and treatment was largely due to the implementation of PSA into everyday clinical practice. This spike was followed by a plateau with an incidence of approximately 160 cases per 100,000 males/year. In the following 10-15 years, PCa mortality has declined slowly (because of the large number of treated patients) and decidedly less than expected.[1] It then became apparent the need to develop tools to better stage and properly stratify patients diagnosed with PCa, in order to offer the most appropriate treatment options. In recent years, it has become widely accepted that prostate cancer treatments offered need to be tailored to the disease of each patient. Improved diagnostics will allow urologists to better understand the natural history of prostate cancer disease. The disease is therefore no longer seen as a static condition, but as the array of its evolutive characteristics, much in the same way a photo differs from a movie. A better understanding of the disease process allows for a more refined treatment and more precise surgical, radiotherapeutic and pharmacological action. We reviewed the literature with focus on offering the Urologist the most up-to-date tools in the decision-making process in patients with PCa.

Evidence acquisition

The current study is a systematic review of the literature conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[2] A systematic and critical analysis through Medline, EMBASE, Scopus and Web of Science databases was carried out by two authors (P.F, L.B.) separately, using the following key words: "prostate cancer," "prediction tools," and "nomograms." The search was conducted across the title and abstract fields of the records, with the following limits: humans, gender (male), and language (English). Only full-text articles were taken into consideration and abstracts were not included.

We decided not to include data from congress abstract proceedings as they might lack the completeness of data we needed. Out of the total number of articles found (N.=1005), only 68 articles were selected for review, and additional 4 studies were manually added. We assessed the methodological quality of studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies, as recommended by Cochrane collaboration. This instrument uses a star system to evaluate observational studies based on three criteria: participant selection, comparability of study groups and assessment of outcome or exposure. A maximum of four stars, two stars, and three stars can be awarded respectively for each category. Studies awarded over 6 points were considered to be of high quality (Figure 1).

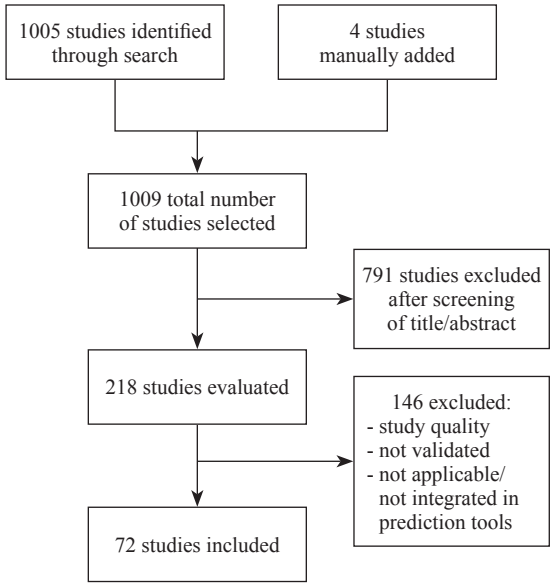

Figure 1.—Flow chart of study inclusion process.

Evidence synthesis

The 72 selected articles have been summarized and grouped according to the clinical phase to which they refer (as indicated in Figure 2). We identified three main chronological steps: 1) before treatment; 2) treatment options; 3) after treatment.

Tools aimed at each phase were further grouped into more specific subsets, according to the peculiar aspect they refer to. The last

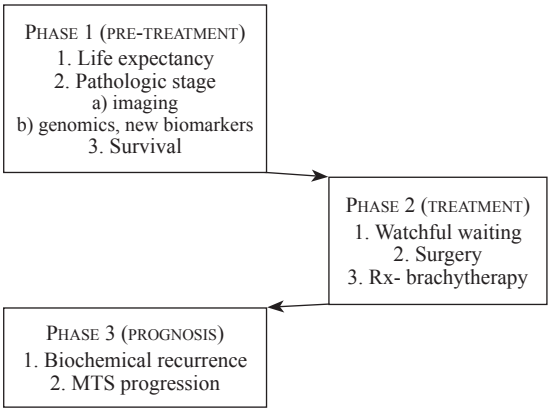

Figure 2.—Grouping of papers for the review according to the clinical phase they refer to.

section is dedicated to the most recent research findings, part of which still needs to be implemented in readily available tools, but already proving to be too effective to be exempted from the present review.

Tools for prediction of life expectancy (before treatment)

Shariat *et al.*[3, 4] reviewed 111 predictive tools for prostate cancer and reported 5 that pertained to life expectancy. Mattew and Vickers reported that most of the tools for prostate cancer were either inappropriate for use in the clinic or provided highly questionable estimates or recommendations, such as surgery for low risk cancer in a substantial proportion of 80-year-olds.[5] Although guidelines consider life expectancy as a criterion for determining treatment options, it is not easy to identify tools that could be appropriately used into a point-of-care decision aid; moreover, age limit for radical prostatectomy is currently debated.[5]

The MALE model [6] needs an abundance of specific comorbidity factors such as angina classification or the level of aortic stenosis. It is not easy to obtain such extensive information at the initial consultation for prostate cancer.[5] Jeldres *et al.*[7] encountered similar problems when evaluating tools that could aid clinicians in predicting life expectancy for prostate cancer patients. Although they report concordance indices ranging from 0.60-0.84, the tools with higher discrimination, those of Walz *et al.*[8] and Cowen *et al.*,[9] both required a treatment to be selected to obtain predictions.

Kim *et al.*[10] also reported on the lack of life expectancy tools being utilized by clinicians. They found that only one in four radiation oncologists or urologists used a formal method for evaluating life expectancy. This finding might best be interpreted as rational behavior, given the lack of appropriate tools.

Tools for prediction of pathological stage (before treatment)

Many models have been proposed to estimate pathologic stage at radical prostatectomy, those tools aid in the treatment planning for new diagnosed patients.[11]

Oesterling *et al.* initially attempted to predict the pathologic stage of clinically localized prostate cancer using logistic regression (LG).[12]

In 1993, Partin *et al*. combined the PSA expression level, clinical classification, and the Gleason Score (GS) to predict the pathologic stage in males treated for clinically localized prostate cancer by a single surgeon at Johns Hopkins Hospital (Baltimore, MD, USA).[13] Partin *et al*.[14-17] subsequently combined the clinical data from three academic institutions and updated the LR-based nomogram to simultaneously predict the pathological stage. The tables were validated in 1997 and 2004.[14, 18] Although the Partin tables represented a landmark in pre-treatment PCa staging, they have limitations. For example, the probability of extracapsular extension (ECE) cannot be predicted in a side-specific fashion.

In order to aid surgical technical planning Graefen *et al.* developed a regression tree capable of predicting ECE in a side-specific manner (SS-ECE),[19] and both Ohori *et al.*[20] (N.=763) and Steuber *et al.*[21] (N.=1118) developed accurate tools to predict SS-ECE (c-index: 79-81% and 84%, respectively).

In 2010, Chung *et al.* (N.=1031) developed a model to predict ECE based upon a population of Korean men who underwent radical prostatectomy for clinically localized PCa.[22] The

model showed good discrimination in the validation cohort (N.=440; AUC=0.782).

In 2012, Caire *et al.* developed from a cohort of 1985 patients a model for determining non-organ confined disease. The model included race, age, body mass index, PSA, biopsy Gleason sum and clinical stage.[23]

Models to predict the probability of seminal vesicles invasion were developed in 2003 by Koh *et al.*[24] and Gallina *et al.*[25] in 2007. In 2012, Lughezzani compared three different tools for prediction of seminal vesicle invasion; they reported that the Partin tables represent the ideal strategy for stratifying the risk of seminal vesical invasion.[26]

In 2006 Briganti *et al.* developed a LNI prediction tool from 602 patients who underwent extended pelvic lymphadenectomy (ePLND) (76% discrimination).[27] In 2012 this model was updated increasing the predictive accuracy for LNI.[28] An interesting model was developed to suspect invasion of exclusive non-obturator lymph node metastasis.[29]

A head-to-head comparison of the National Comprehensive Cancer Network (NCCN) practice guideline lymph node invasion (LNI) nomogram,[30] Partin tables,[16] and D'Amico risk-classification [31] was conducted by Abdollah *et al*. for prediction of LNI at radical prostatectomy (RP).[32] The NCCN nomogram provided the greatest discrimination (AUC=82%), and decision-curve analysis demonstrated that this model had the highest net-benefit for threshold probabilities ≥4%. However, for a threshold probability for LNI<4%, the Partin tables provided the greatest net-benefit.

The role of magnetic resonance imaging (MRI) in prostate cancer staging has been emerging with improved MR techniques. Current PCa mpMRI techniques vary, and this results in the lack of an unequivocal, widely accepted standard both in image acquisition/elaboration as well as in clinical interpretation.

Feng *et al.*[33] compared the accuracy of mpMRI against the Partin tables and Memorial Sloan Kettering (MKS) nomogram for predicting ECE (N.=112), and developed a tool to estimate pathologic ECE risk. When adding mpMRI to the ECE prediction tools, AUC increased significantly (Partin from 0.85 to 0.92; MSK from 0.86 to 0.94). mpMRI proved more successful in predicting ECE by 15-40% when compared to the clinical nomograms.

Radtke *et al.*[34] investigated the role of MRI in predicting ECE, SVI, and negative surgical margins at RP, in different PCa risk groups of patients (N.=132), trying to define a standard, and retrospectively investigated ESUR score for ECE and SVI. Their work showed how standardized ECE scoring on mpMRI is an independent predictor of pT3 disease and may be useful in planning RP with improved oncologic security, including in high-risk patients. Moreover, it helps to accurately select a subgroup of patients for systematic MRI-guided intraoperative frozen sections.

In 2006, Wang *et al.*[35] investigated the value of endorectal coil MR imaging and combined endorectal MR imaging MR spectroscopic imaging to the staging nomograms for predicting organ-confined prostate cancer.[15] The model including MRI variables (presence of ECE or SVI) had significantly better discriminative ability than did the base model (AUC=0.892 *vs*. 0.633, respectively; P<0.01).

In 2007, Wang evaluated whether endorectal MR imaging findings contribute to increase value to the Kattan nomogram [24] for predicting SVI in patients with prostate cancer. In fact, the Kattan nomogram plus endorectal MR imaging (0.87) had a significantly larger (P=0.05) AUC than either endorectal MR imaging alone (0.76) or the Kattan nomogram alone (0.80).

More recently de Rooij *et al.*[36] elaborated a meta-analysis on MRI, proving that it appears to have a high specificity but poor and heterogeneous sensitivity for detection of ECE, SVI, and overall stage T3, but it is not satisfying to accurately stage local PCa. They also showed how prediction of the correct T stage can be improved when MRI findings are combined with other clinical data (such as the D'Amico risk categories).

Tools for prediction of biochemical recurrence (before/after treatment)

Biochemical recurrence (BCR) is defined as 2 consecutive serum PSA values >0.2 ng/mL

after radical prostatectomy; after radiation therapy, a rising PSA level 2.0 ng/mL above the nadir value, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.[37]

Pre-surgical prediction of BCR was first addressed by Kattan *et al.*[38] with the development of a nomogram to predict 5-year biochemical recurrence (BCR) for patients treated with RP. Accuracy of 75% (65-83%) was confirmed on external validation.[39-41] However, since pre-requirement for surgical treatment of PC is a life expectancy >10 years, the 5-year follow-up time is an insufficient prediction. Their work was later updated by Stephenson *et al.*[42] with a follow-up of 10 years (77% discrimination). Suardi *et al.*[43] developed a prediction tool that extends to 20 years after RP, accounting for disease-free interval (77-83% discrimination, confirmed in two external validation cohorts).

Seo *et al*.[44] validated the CAPRA-s for recurrence-free survival in a cohort of 115 Korean men treated by a single surgeon. They defined BCR as 2 consecutive PSA values ≥0.2 ng/mL. They studied the cohort with the seven-group model (each CAPRA score sum) and three-group model (low, intermediate, and high risk). The CAPRA score showed high accuracy in prediction of recurrence-free survival (c-index 0.74, 0.77, respectively), thus it was suggested to aid Urologists in planning treatment for localized PCa.

Most recently, Hu *et al.*,[45] studying a cohort of 1656 men, developed an artificial neural network (ANN) to predict BCR, and compared it with a logistic regression (LR) model; the AUC was 0.754 for ANN and 0.755 for the LR model, and suggested that combination of GS and ANN output value, the BCR prediction is more accurate especially for high-risk patients with GS≥7.

Deng *et al.*,[46] starting from the recent acquisition that the risk of BCR after RP for pathologic GS 7 directly relates to the proportion of the GS 4 component, analyzed 2630 radical prostatectomy patients and determined that 3 quantitative measures of GS 4 pattern (proportion of tumor composed of GS 4, prostate size weighted score considering the global quantity of GS 4, and the quantity of GS 4 in the index lesion) predict BCR better than the traditional GS (c-index 0.83-0.84, *vs*. traditional GS 0.82).

Tools for prediction of survival and cancer-specific mortality (before/after treatment)

PCa-specific mortality (PCSM) is the single most important cancer-control endpoint in RP candidates. To assess this issue, D'Amico *et al*.[47] and Cooperberg *et al*.[48] developed risk stratifications tools to predict PCSM, returning 80% discrimination in internal validation.

A meta-analysis comparing the 5 available tools, showed how the model developed by Stephenson *et al*.,[49] and externally validated in a large cohort of patients (N.=6278, discrimination 82%), outperformed other tools, making it the preferred choice.[26] This nomogram evaluates biopsy Gleason grade, PSA, and clinical stage.

Korets *et al*.[50] evaluated accuracy of the Kattan nomogram across all PCa risk groups. They stratified the cohort (N.=1877) according to D'Amico risk criteria, and compared the nomogram with actuarial Kaplan-Meier survival statistics. They confirmed accurate prediction of survival across all PCa risk groups (c-index 0.67) although prediction ability varied by risk group. Similarly to the D'Amico model, c-index increased to 0.69 when intermediate-risk patients were removed from the model.

Cooperberg *et al.*[51] compared CAPRA-s and the Decipher GC in order to predict PCSM in a cohort of post-RP patients who experienced CSM (cohort N.=185, CSM N.=28). The models were evaluated individually and compared for prediction of CSM (c-index, decision-curve analysis, reclassification, cumulative incidence, Cox regression). C-indexes were 0.75 for CAPRA-s, 0.78 for GC. Moreover, GC returned higher net-benefit on decision-curve analysis, but the combination score of CAPRA-s and GC did not improve the AUC after optimism-adjusted bootstrapping. They concluded that patients with both CAPRA-s and GC high risk scores have a significantly elevated post-RP risk for lethal PCa.

As for EBRT, Kattan *et al*.[52] studied a cohort of 1677 patients to devise a pre-treatment nomogram to predict probability of MTS at 5 years following EBRT, evaluating PSA clinical stage, biopsy Gleason sum; this was externally validated and showed excellent discrimination (N.=1626, c-index 81%).

Tools for prediction of metastatic progression (after treatment)

Men diagnosed with similar PCa often develop significantly variable outcomes after radical local therapy, even those classified at a high risk of recurrence. Tools for predicting metastatic progression are crucial in evaluating adequate post-surgery treatment.

Current tools for prediction of metastatic progression stemmed from the need of a more complete predictive ability, rather than only predicting Gleason sum upgrade or BCR. Cooperberg *et al.*[48] evaluated the CAPRA-s, assessing its accuracy in predicting metastatic progression. Studying a large cohort (N.=10,627) of men with clinically localized PCa, they proved how every single point increase in the CAPRA score, associates with increased bone metastases (HR for bone metastasis 1.47, 95% CI: 1.39-1.56). Therefore, the CAPRA score is accurate in predicting metastases (c-index 0.78).

Porter *et al*.[53] developed and internally validated a post-treatment nomogram (N.=752) that indicated pathological stage T3, elevated pathological Gleason sum as independent predictors of metastatic progression. Their model showed accuracy of 80.2, 77.7, 77.6, and 76.0 at 5, 10, 15, and 20 years after prostatectomy, respectively.

Lindberg *et al.*[54] remarked how metastatic PCa is a monoclonal disease, and how prognosis prediction is connected to intraprostatic tumor heterogeneity, and suggested intraductal carcinoma as a marker of aggressive disease. Tools integrating this aspect have yet to be developed.

Perera *et al.*[55] elaborated a meta-analysis on ^{68}Ga prostate-specific membrane antigen positron-emission tomography. The results indicated favorable sensitivity and specificity profiles compared to choline-based PET imaging techniques.

Biomarkers and genomics

Genomics classifiers

Genomic tests measure biological markers in the tumor. Whereas a test for PSA provides information about a single molecular marker, genomic tests evaluate more than a million molecular markers, improving the detection of aggressive PCa. This information can be useful in after surgery decision-making.

Paris *et al.*[56] developed the GEMCaP genomic classifier to improve prediction of metastatic PCa in a high-risk cohort. This resulted in outperforming the prediction of the Kattan nomogram in negative lymph nodes high-risk patients. This is where the nomogram has weakness and suggests that the inclusion of this tool may improve results (improving the AUROC from 0.81 to 0.84-0.85).

Oh *et al*.[57] used exome genotyping to predict pathological GS upgrade in low-risk RP patients (N.=257). Their results found that 15 single nucleotide repeats (SNPs) were significant in predicting GS upgrade in low-risk PCa patients; but one SNP remained significant after multiple testing. They later added this into a multivariate model (PSA, biopsy GS, Positive core number, tumor per core ratio, and age) improving the accuracy of prediction from 78.4% to 82.9% (P=0.0196).

Marrone *et al*.[58] reviewed the available data of a genomic classifier based on 22-gene expression assay, developed to predict 5-year risk of metastatic progression of PCa in post RP patients.

The Decipher genomic classifier is an extensively validated genomic classifier, for postoperative risk prediction of metastasis and PCa mortality. The Decipher result is reported as a percentage risk of metastasis that categorizes PCa as either high or low risk based on the genomics of their individual cancer. However, in terms of clinical utility, no evidence was found regarding improved outcomes (defined

as lowered CSM and treatment related adverse effects) from using the GC results to guide post-RP treatment, and they suggested further clinical evidence is required to show improved clinical outcomes.

This allows for a clear step towards a tailored approach, through an improvement in risk stratification that distinguishes local from systemic disease, as genomic identification allows for personalized treatment.

Klein *et al*.[59] tested in a cohort of 169 men with postoperative high risk PCa (pT3, PSA>20 ng/L, or positive margin) and proved how adding the Decipher classifier to common risk-stratifications tools (CAPRA score and Stephenson nomogram) increases the accuracy of prediction of rapid metastasis (metastatic disease within 5 years after surgery, N.=15) and non-rapid metastasis (N.=154). The Decipher test proved to be a significant predictor (c-index 0.77), outperforming both Stephenson (0.75) and CAPRA-s (0.72). Integration of Decipher test into the Stephenson nomogram increased prediction for metastatic progression (c-index 0.79), suggesting it as a validated tool for identification of patients with increased risk of developing metastatic disease. This information can then be used to involve patients with multimodality therapy.

Klein *et al*.[60] recently applied the Decipher classifier to prostate biopsies, in order to predict metastasis risk (N.=57). The performance evaluation was performed with a Cox multivariable proportional hazard model, and survival C-index. The Decipher plus NCCN model (National Comprehensive Cancer Network) had improved the c-index of 0.88 compared to NCCN alone (c-index 0.75). Moreover, on a multivariate analysis, Decipher was the only significant predictor when adjusted for confounding factors. The limited number of patients in this study needs further validation.

Ross *et al*.[61] tested the Decipher GC in post RP high-risk patients (N.=356) who did not receive additional treatment until the time of metastatic progression. Decipher scores were obtained in 260 patients, of whom 99 experienced metastasis. Their results showed how Decipher scores correlated with increased cumulative incidence of BCR, metastasis, and PCa specific mortality (P<0.01). Moreover, inclusion of the Decipher score into validated clinico-pathological models improved their prognostic performance.

The Oncotype DX Prostate Cancer Assay is a multi-gene RT-PCR expression assay specifically designed for use with prostate needle biopsies. It measures expression of 12 cancer-related genes representing four biological pathways and 5 reference genes which are combined to calculate the Genomic Prostate Score (GPS). This biopsy-based assay has been analytically and subsequently clinically validated as a predictor of aggressive prostate cancer. Results from Knezevic *et al.*[62] showed how it is a robust and reliable assay that enables improved decision making for patients with early-stage PCa.

In 2014 Sommariva *et al.*[63] elaborated a meta-analysis on the cell cycle progression (CCP) score (Prolaris). The CCP is an RNA expression signature based on analysis of 31 genes that determine cancer aggressiveness of PCa and predict the probability of disease progression. Their results show how the CCP score highlights the aggressive potential of an individual's PCa outperforming existing assessment tools.

Urinary biomarkers

Recent research in detection of PCa and discrimination from BPH at the molecular level, is exploring microRNA urinary traces of PCa. Salido-Guadarrama *et al.*[64] identified and validated a urinary microRNA-based signature (miR-100/200b) to enhance the specificity of PCa diagnosis to overcome the limits of serum PSA They developed a model that includes age, prostate-specific antigen (PSA), percentage of free PSA and DRE, and a second model enriched with the miR-100/200b signature. The combined model significantly outperformed the capacity of both PSA (P<0.001) and the base model (P=0.01) in discriminating PCa from BPH patients. Decision curve analysis showed that the combined model improved the clinical benefit for patients and produced

a substantial reduction in unnecessary (BPH) biopsies across a range of reasonable threshold probabilities (10-50%)

Van Neste *et al.*[65] focused on detection of clinically significant PCa, and developed a multimodal model (N.=519) and validated it on a different cohort (N.=386), incorporating messenger RNA (mRNA) biomarkers and traditional risk factors in order to identify patients with biopsy high-grade PCa (GS≥7). Two microRNA (HOXC6 and DLX1) levels performed as good predictors for detection of high-grade PCa. Overall AUC of the multimodal model was 0.90 (95% CI: 0.85-0.95) in the validation cohort and 0.86 in the first cohort. A second model included DRE and reached AUC of 0.86 (95% CI: 0.80-0.92; AUC 0.90 in the first cohort). Both models were successfully validated, with no significant change in AUC in validation. DCA indicated a strong net benefit and the best reduction in unnecessary biopsies compared with other clinical decision-making tools, such as the Prostate Cancer Prevention Trial risk calculator and the PCA3 assay.

While promising, these new tests still need to prove their analytical and clinical validity; urging for larger and prospective studies to compare them thoroughly and test their value in clinical management of PCa is necessary. Furthermore, the field of these new approaches to PCa is rapidly and continuously evolving, likely leaving some of these new tools to be abandoned and substituted by yet to be discovered ones.[66]

Discussion

PCa is a very complex disease, and the multitude of studies and predictive and prognostic tools available, while increasing tailoring possibilities, complicates clinical decisions, in diagnostic as well as in treatment and post-treatment decisions. Existing models allow the clinicians to provide an evidence-based approach, offering individualized treatment options for each patient. This has been shown to yield better results than intuitive clinical decision-making.[67, 68] The available information needs therefore to be organized and filtered by the Urologist, and provided to the patient to inform him of accurate predictions and likely outcomes and possible side-effects connected to each management option. Only in this fashion can the clinician offer a personalized treatment and the best QoL.

Nomograms are currently the most accurate prediction tools available, however, several of them are lacking external validation This renders them susceptible to limitations when applied to different populations from the one adopted for their development. After PCa diagnosis is first made, prediction of life expectancy needs to be taken in consideration as a first step, however the available tools are generally underused because of their poor performance.[10] Prediction of pathological stage of the disease is also very challenging, and the available tools are undergoing a rapid evolution since the integration of mpMRI scores in the available nomograms, returning significantly improved accuracy.[36]

The interest for active surveillance is increasing in very-low and low risk disease.[69] The prediction of pathological stage of the disease plays an important role to guide treatment decisions in low risk PCa, an example is the recent study in which candidates for active surveillance had a good oncological outcome despite upstaging on final pathological stage.[70]

Competing risks also pose a very delicate issue: life expectancy, BCR and CSM need to be predicted with distant end-points, while most studies are limited to 5-year follow-up, which is inadequate for quality planning. BCR is crucial in deciding whether adjuvant therapy is needed: the 20-year follow-up Suardi nomogram proved to be accurate, and more recently proportion of GS 4 in index lesion has been shown to be a simple and reliable predictor of BCR. While the final benchmark for effectiveness of a tool is the clinical consequences, the quality of a nomogram should be evaluated by its accuracy.[71] Cancer specific mortality is the most important single endpoint in PCa: CAPRA-s has been validated as a well performing tool, and when integrated with genomic classifiers (Decipher) helps identifying patients with significantly elevated risk for lethal PCa. Risk

of metastatic progression has been assessed accurately by the CAPRA-s, and recently, the CCP GC was validated as outperforming the CAPRA-s in prediction of aggressiveness and MTS progression risk.

The number of available tools poses the Urologists with the choice of which tools to apply: Nguyen and Kattan [72] tried to ease the issue by building a metagram of the available tools, stratifying them by accuracy, quality, and usefulness in the clinical setting. The available tools analyzed 16 possible treatment options and 10 outcomes of cancer control, survival and morbidity. Of the 160 treatment/outcome combinations, only 31 possibilities are addressed by available tools, suggesting that many more are needed; moreover, the flexibility of predictive and prognostic tools needs to be improved, as clinicians may not access all the variables needed to employ the tools.

Besides the difficulties and lacking evidence in evaluating the clinical benefit of many of the prediction models, decision-making should be centered on enhanced modeling that includes new biomarkers, diagnostic imaging, longer time frames for predicted outcomes, and is focused on QoL.

Moreover, with the advent of new therapeutic options, such as RALP, LARP, HIFU and focal ablative therapy, tools should be developed to specifically evaluate each approach, and its implications when combined with the currently available options.

Conclusions

Currently available tools are of great help in shaping the decision-making process of the Urologist in every step from the first elevated PSA to the surgical and post-treatment phases, however, only the integration of multiple tools allows for a proper care of each patient.

At present, most of the available tools based upon clinical and pathological variables still leave an open gap; in fact, non-high-risk tumors may lead to an extremely malignant evolution, whereas some high-grade tumors follow a more benign path. The current development of new powerful resources, such as genomic tests, microRNA and mpMRI, will most likely in the very near future alter deeply the way PCa is understood, diagnosed, identified, classified and accordingly treated. These tools will lead to more tailored approach to prostate cancer management.

References

1. Abdollah F, Schmitges J, Sun M, Tian Z, Briganti A, Shariat SF, *et al.* A critical assessment of the value of lymph node dissection at radical prostatectomy: A population-based study. Prostate 2011;71:1587-94.
2. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
3. Shariat SF, Karakiewicz PI, Roehrborn CG, Kattan MW. An updated catalog of prostate cancer predictive tools. Cancer 2008;113:3075-99.
4. Shariat SF, Karakiewicz PI, Margulis V, Kattan MW. Inventory of prostate cancer predictive tools. Curr Opin Urol 2008;18:279-96.
5. Kent M, Vickers AJ. A systematic literature review of life expectancy prediction tools for localized prostate cancer patients. J Urol 2015;193:1938-42.
6. Clarke MG, Kennedy KP, MacDonagh RP. Development of a clinical prediction model to calculate patient life expectancy: the measure of actuarial life expectancy (MALE) Med Decis Making 2009;29:239-46.
7. Jeldres C, Latouff JB, Saad F. Predicting life expectancy in prostate cancer patients. Curr Opin Support Palliat Care 2009;3:166-9.
8. Walz J, Gallina A, Saad F, Montorsi F, Perrotte P, Shariat SF, *et al.* A nomogram predicting 10-year life expectancy in candidates for radical prostatectomy or radiotherapy for prostate cancer. J Clin Oncol 2007;25:3576-81.
9. Cowen ME, Halasyamani LK, Kattan MW. Predicting life expectancy in men with clinically localized prostate cancer. J Urol 2006;175:99-103.
10. Kim SP, Karnes RJ, Nguyen PL, Ziegenfuss JY, Han LC, Thompson RH, *et al.* Clinical implementation of quality of life instruments and prediction tools for localized prostate cancer: results from a national survey of radiation oncologists and urologists. J Urol 2013;189:2092-8.
11. Green DA, Osterberg EC, Xylinas E, Rink M, Karakiewicz PI, Scherr DS, *et al*. Predictive tools for prostate cancer staging, treatment response and outcomes. Arch Esp Urol 2012;65:787-807.
12. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J Urol 1991;145:907-23.
13. Partin AW, Yoo J, Carter HB, Pearson JD, Chan DW, Epstein JI, *et al*. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J Urol 1993;150:110-4.
14. Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, Oesterling JE, *et al.* Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update [published erratum appears in JAMA 1997;278:118].
15. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer

staging nomograms (Partin Tables) for the new millennium. Urology 2001;58:843-8.
16. Makarov DV, Trock BJ, Humphreys EB, Mangold LA, Walsh PC, Epstein JI, *et al.* Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. Urology 2007;69:1095-101.
17. Eifler JB, Feng Z, Lin BM, Partin MT, Humphreys EB, Han M, *et al*. An updated prostate staging nomogram (Partin tables) based on cases from 2006 to 2011. BJU Int 2013;111:22-9.
18. Augustin H, Eggert T, Wenske S, Karakiewicz PI, Palisaar J, Daghofer F, *et al.* Comparison of accuracy between the Partin tables of 1997 and 2001 to predict final pathological stage in clinically localized prostate cancer. J Urol 2004;171:177.
19. Graefen M, Haese A, Pichlmeier U, Hammerer PG, Noldus J, Butz K, *et al.* A validated strategy for side specific prediction of organ confined prostate cancer: a tool to select for nerve sparing radical prostatectomy. J Urol 2001;165:857.
20. Ohori M, Kattan MW, Koh H, Maru N, Slawin KM, Shariat S, *et al.* Predicting the presence and side of extracapsular extension: a nomogram for staging prostate cancer. J Urol 2004;171:1844.
21. Steuber T, Graefen M, Haese A, Erbersdobler A, Chun FK, Schlom T, *et al.* Validation of a nomogram for prediction of side specific extracapsular extension at radical prostatectomy. J Urol 2006;175:939.
22. Chung JS, Choi HY, Song HR, Byun SS, Seo Si, Song C, *et al.* Preoperative nomograms for predicting extracapsular extension in Korean men with localized prostate cancer: a multi-institutional clinicopathologic study. J Korean Med Sci 2010;25:1443.
23. Caire AA, Sun L, Lack BD, Lum K, Tang P, Albala DM, *et al.* Predicting non-organ-confined prostate cancer in men diagnosed after 2000. Prostate Cancer Prostatic Dis 2010;13:248-51.
24. Koh H, Kattan MW, Scardino PT, Suyama K, Maru N, Slawin K, *et al.* A nomogram to predict seminal vesicle invasion by the extent and location of cancer in systematic biopsy results. J Urol 2003;170:1203.
25. Gallina A, Chun FK, Briganti A, Shariat SF, Montorsi F, Salonia A, *et al.* Development and split-sample validation of a nomogram predicting the probability of seminal vesicle invasion at radical prostatectomy. Eur Urol 2007;52:98.
26. Lughezzani G, Zorn KC, Budäus L, Sun M, Lee DI, Shalhav AL, *et al.* Comparison of three different tools for prediction of seminal vesicle invasion at radical prostatectomy. Eur Urol 2012;62:590-6.
27. Briganti A, Chun FK, Salonia A, Zanni G, Scattoni V, Valiquette L, *et al.* Validation of a nomogram predicting the probability of lymph node invasion among patients undergoing radical prostatectomy and an extended pelvic lymphadenectomy. Eur Urol 2006;49:1019.
28. Briganti A, Larcher A, Abdollah F, Capitanio U, Gallina A, Suardi N, *et al.* Updated nomogram predicting lymph node invasion in patients with prostate cancer undergoing extended pelvic lymph node dissection: the essential importance of percentage of positive cores. Eur Urol 2012;61:480.
29. Briganti A, Chun FK, Salonia A, Zanni G, Gallina A, Dehò F, *et al.* A nomogram for staging of exclusive non-obturator lymph node metastases in men with localized prostate cancer. Eur Urol 2007;51:112.
30. Cagiannos I, Karakiewicz P, Eastham JA, Ohori M, Rabbani F, Gerigk C, *et al.* A preoperative nomogram identifying decreased risk of positive pelvic lymph nodes in patients with prostate cancer. J Urol 2003;170:1798.
31. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, *et al.* Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969.
32. Abdollah F, Schmitges J, Sun M, Thuret R, Djahangirian O, Tian Z, *et al.* Head-to-head comparison of three commonly used preoperative tools for prediction of lymph node invasion at radical prostatectomy. Urology 2011;78:1363.
33. Feng TS, Sharif-Afshar AR, Wu J, Li Q, Luthringer D, Saouaf R, *et al.* Multiparametric MRI Improves Accuracy of Clinical Nomograms for Predicting Extracapsular Extension of Prostate Cancer. Urology 2015;86:332-7.
34. Radtke JP, Hadaschik BA, Wolf MB, Freitag MT, Schwab C, Alt C, *et al.* The Impact of Magnetic Resonance Imaging on Prediction of Extraprostatic Extension and Prostatectomy Outcome in Patients with Low-, Intermediate- and High-Risk Prostate Cancer: Try to Find a Standard. J Endourol 2015;29:1396-405.
35. Wang L, Hricak H, Kattan MW, Schwartz LH, Eberhardt SC, Chen HN, *et al.* Combined endorectal and phased-array MRI in the prediction of pelvic lymph node metastasis in prostate cancer. AJR Am J Roentgenol 2006;186:743.
36. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. Eur Urol 2016;70:233-45.
37. Mottet N, Bellmunt J, Briers E, Bolla M, Bourke L, Cornford P, *et al*.; European Association of Urology. Prostate cancer guidelines; 2017 [Internet]. Available from: https://uroweb.org/guideline/prostate-cancer/#7 section [cited 2017, May 16].
38. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. J Natl Cancer Inst 1998;90:766-71.
39. Graefen M, Karakiewicz PI, Cagiannos I, Hammerer PG, Haese A, Palisaar J, *et al.* A validation of two preoperative nomograms predicting recurrence following radical prostatectomy in a cohort of European men. Urol Oncol 2002;7:141-6.
40. Graefen M, Karakiewicz PI, Cagiannos I, Quinn DI, Henshall SM, Grygiel JJ, *et al.* International validation of a preoperative nomogram for prostate cancer recurrence after radical prostatectomy. J Clin Oncol 2002;20:3206-12.
41. Bianco FJ Jr, Kattan MW, Scardino PT, Powell IJ, Pontes JE, Wood DP Jr. Radical prostatectomy nomograms in black American men: accuracy and applicability. J Urol 2003;170:73-6; discussion 76-7.
42. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ Jr, Dotan ZA, Fearn PA, *et al*. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. J Natl Cancer Inst 2006;98:715-7.
43. Suardi N, Porter CR, Reuther AM, Walz J, Kodama K, Gibbons RP, *et al.* A nomogram predicting long-term biochemical recurrence after radical prostatectomy. Cancer 2008;112:1254-63.
44. Seo WI, Kang PM, Chung JI. Predictive value of the cancer of the prostate risk assessment score for recurrence-free survival after radical prostatectomy in Korea: a single-surgeon series. Korean J Urol 2014;55:321-6.
45. Hu XH, Cammann H, Meyer HA, Jung K, Lu HB, Leva N, *et al.* Risk prediction models for biochemical recurrence after radical prostatectomy using prostate-specific antigen and Gleason score. Asian J Androl 2014;16:897-901.
46. Deng FM, Donin NM, Pe Benito R, Melamed J, Le Nobin J, Zhou M, *et al.* Size-adjusted Quantitative Gleason

Score as a Predictor of Biochemical Recurrence after Radical Prostatectomy. Eur Urol 2016;70:248-53.
47. D'Amico AV, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. J Clin Oncol 2002;20:4567-73.
48. Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastasis and mortality at the time of diagnosis. J Natl Cancer Inst 2009;101:878-87.
49. Stephenson AJ, Kattan MW, Eastham JA, Bianco FJ Jr, Yossepowitch O, Vickers AJ, *et al.* Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. J Clin Oncol 2009;27:4300-5.
50. Korets R, Motamedinia P, Yeshchina O, Desai M, McKiernan JM. Accuracy of the Kattan nomogram across prostate cancer risk-groups. BJU Int 2011;108:56-60.
51. Cooperberg MR, Davicioni E, Crisan A, Jenkins RB, Ghadessi M, Karnes RJ. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. Eur Urol 2015;67:326-33.
52. Kattan MW, Zelefsky MJ, Kupelian PA, Cho D, Scardino PT, Fuks Z, *et al.* Pretreatment nomogram that predicts 5-year probability of metastasis following three-dimensional conformal radiation therapy for localized prostate cancer. J Clin Oncol 2003;21:4568-71.
53. Porter CR, Suardi N, Kodama K, Capitanio U, Gibbons RP, Correa R, *et al.* A nomogram predicting metastatic progression after radical prostatectomy. Int J Urol 2008;15:889-94.
54. Lindberg J, Kristiansen A, Wiklund P, Grönberg H, Egevad L. Tracking the origin of metastatic prostate cancer. Eur Urol 2015;67:819-22.
55. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, *et al.* Sensitivity, Specificity, and Predictors of Positive ^{68}Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016;70:926-37.
56. Paris PL, Weinberg V, Albo G, Roy R, Burke C, Simko J, *et al*. A group of genome-based biomarkers that add to a Kattan nomogram for predicting progression in men with high-risk prostate cancer. Clin Cancer Res 2010;16:195-202.
57. Oh JJ, Park S, Lee SE, Hong SK, Lee S, Choe G, *et al.* The use of exome genotyping to predict pathological Gleason score upgrade after radical prostatectomy in low-risk prostate cancer patients. PLoS One 2014;9:e104146.
58. Marrone M, Potosky AL, Penson D, Freedman AN. A 22 Gene-expression Assay, Decipher® (GenomeDx Biosciences) to Predict Five-year Risk of Metastatic Prostate Cancer in Men Treated with Radical Prostatectomy. PLoS Curr 2015 Nov 17;7.
59. Klein EA, Haddad Z, Yousefi K, Lam LL, Wang Q, Choeurng V, *et al.* Decipher Genomic Classifier Measured on Prostate Biopsy Predicts Metastasis Risk. Urology 2016;90:148-52.
60. Klein EA, Yousefi K, Haddad Z, Choeurng V, Buerki C, Stephenson AJ, *et al.* A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. Eur Urol 2015;67:778-86.
61. Ross AE, Johnson MH, Yousefi K, Davicioni E, Netto GJ, Marchionni L, *et al.* Tissue-based Genomics Augments Post-prostatectomy Risk Stratification in a Natural History Cohort of Intermediate- and High-Risk Men. Eur Urol 2016;69:157-65.
62. Knezevic D, Goddard AD, Natraj N, Cherbavaz DB, Clark-Langone KM, Snable J, *et al*. Analytical validation of the Oncotype DX prostate cancer assay - a clinical RT-PCR assay optimized for prostate needle biopsies. BMC Genomics 2013;14:690.
63. Sommariva S, Tarricone R, Lazzeri M, Ricciardi W, Montorsi F. Prognostic Value of the Cell Cycle Progression Score in Patients with Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016;69:107-15.
64. Salido-Guadarrama AI, Morales-Montor JG, Rangel-Escareño C, Langley E, Peralta-Zaragoza O, Cruz Colin JL, *et al.* Urinary microRNA-based signature improves accuracy of detection of clinically relevant prostate cancer within the prostate-specific antigen grey zone. Mol Med Rep 2016;13:4549/60.
65. Van Neste L, Hendriks RJ, Dijkstra S, Trooskens G, Cornel EB, Jannink SA, *et al.* Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. Eur Urol 2016;70:740-8.
66. Falzarano SM, Ferro M, Bollito E, Klein EA, Carrieri G, Magi-Galluzzi C. Novel biomarkers and genomic tests in prostate cancer: a critical analysis. Minerva Urol Nefrol 2015;67:211-31.
67. Ross PL, Gerigk C, Gonen M, Yossepowitch O, Cagiannos I, Sogani PC, *et al.* Comparisons of nomograms and urologists' predictions in prostate cancer. Semin Urol Oncol 2002;20:82-8.
68. Walz J, Gallina A, Perrotte P, Jeldres C, Trinh QD, Hutterer GC, *et al*. Clinicians are poor raters of life-expectancy before radical prostatectomy or definitive radiotherapy for localized prostate cancer. BJU Int 2007;100:1254-8.
69. Weerakoon M, Papa N, Lawrentschuk N, Evans S, Millar J, Frydenberg M, *et al*. The current use of active surveillance in an Australian cohort of men: a pattern of care analysis from the Victorian Prostate Cancer Registry. BJU Int 2015;115(Suppl 5):50.
70. Imnadze M, Sjoberg DD, Vickers AJ. Adverse Pathologic Features at Radical Prostatectomy: Effect of Preoperative Risk on Oncologic Outcomes. Eur Urol 2016;69:143-8.
71. Green DA, Osterberg EC, Xylinas E, Rink M, Karakiewicz PI, Scherr DS, *et al.* Predictive tools for prostate cancer staging, treatment response and outcomes. Arch Esp Urol 2012;65:787-807.
72. Nguyen CT, Kattan MW. Development of a prostate cancer metagram: a solution to the dilemma of which prediction tool to use in patient counseling. Cancer 2009;115(13 Suppl):3039-45.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Article first published online: March 30, 2017. - Manuscript accepted: March 20, 2017. - Manuscript revised: March 14, 2017. - Manuscript received: October 11, 2016.