Editorial

Radical Prostatectomy for High Risk Prostate Cancer: the Role of Contemporany Predictive Models in Clinical Practice

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Abstract

Introduction. Despite advances in molecular medicine, prostate cancer remains the most important medical problem facing the male population and the second most common cause of cancer-related mortality for men in many countries. Moreover, prostatecancer exhibits tremendous variability in clinical behavior, ranging from indolent to aggressive tumors and patients with PSA ≥ 20ng/ml or Gleason score ≥8 or clinical tumor stage stage≥2c who have undergone a curative treatment such as radical prostatectomy may have to face the high risk of recurrence or metastatic progression. Therefore, it is very important to identify patients with one or more adverse clinicopathologic features reflecting unfavorable prognostic outcomes. A number of variables were extensively studied and could be potentially used to identify agressive tumor behaviour and improve the accuracy of outcome prediction for patients with localized prostate cancer. Furthermore,researchers created predictive toolsthat incorporate several pre- and post-operative clinicopathological parametersto optimeze their prognostic value and improve clinical decision making.
Objective. To give a brief overview of data focusing on the predictive toolsfor men with high risk PCa treated by radical prostatectomy for more accurate risk stratification and immediate impact on difficult clinical-making decision.
Conclusions. While the performance of currently predictive models is encouraging, further improvement by inclusion of new prognostic biomarkers in the development of maybe more sophisticated predictive models as well as external validation of their clinical utility in larger data set is imperative.

Keywords: radical prostatectomy, prostate cancer, predictive models, Gleason score

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Introduction

Prostate cancer (PCa) is a major health problem in modern society, and its prevalence is continuously increasing. Furthermore, PCa is currently the second most common cause of cancer death in men(1). Incidence of localized forms of PCa is increasing mainly due to PSA screening and multicore schemes of prostate biopsy. For localized prostate cancer, treatment options range from active surveillance/watchful waiting to radical therapies as radical prostatectomy (RP) or radiation (2). However, patients classified with high risk PCa are at increased risk of positive lymph nodes, disease recurrence or metastatic progression probably due to the presence of micrometastases at the time of diagnosis (3). Therefore, RP alone has been discouraged in this patient category. In addition, these patients have to accept treatment related complications, some with detrimental impact upon their quality of life. Secondary therapies such as radiation therapy or androgen deprivation become especially important due to the lack of identification of subpopulations of patients who are most likely to respond to a specific first-line therapy with curative intent. Moreover, multimodality approaches such as chemotherapy and novel therapeutics before RP are investigated in clinicians effort to improve cancer control (4). In conclusion, there is no consensus for optimal treatment of men with high risk PCa and treatment decisions are complicated by the biologic heterogeneity of the disease.

Today, clinicians should be able to better stratify these patients at the time of diagnosis into poor and good prognosis sets and predict the probability of disease recurrence, risk of metastases or cancer-specific mortality for each patient. Therefore, various predictive models were designed to assist physicians with difficult clinical making decision in the management of high risk PCa and help patients to better understand their disease and choose treatment after an appropriate informed consent.Predictive models are created and ideally validated to predict the future probability that a patient will achieve a particular endpoint.The predictions are derived from hundreds of patients who presented with same characteristics and the choice of a predictive model depends on the outcome to be predicted.

Numerous predictive models relating to PCa staging, treatment response and outcomes have been described (5,6). However, classification nomograms that incorporate several preoperative and postoperative parameters are generally recognized as the most efficient clinically useful models currently available for prediction of disease recurrence after therapy with curative intent for localized prostate cancer.

Despite encouranging results from several validated nomogramsover clinician decisionsusually based on the knowledge and experience of each clinician, further improvements for the development of a reliable model and a personalized clinical approach is critical in the management of clinically relevant disease. Initially, nomogams were developed by using clinical and pathological variables alone. To improve the outcome prediction for patients treated with RP, the clinical potential of PCa molecular biomarkers was investigated, so that a rationale strategy for treatment decisions can be established (7).

The aim of this article was to give a brief overview of data focusing on the predictive tools for patients with high risk PCatreated byRP for more accurate risk stratification and immediate impact on difficult clinical-making decision.

Pre and postoperative predictive models

At present, the definition of high risk PCa remains controversial (European Association Urology guidelines, Radiation Therapy Oncology Group, national comprehensive cancer network, Cancer of the Prostate Risk Assesment score and this lack of consensus represent a critical barrier for comparative assesment of treatment outcomes, patients counceling or designed clinical trials (8, 9, 10). Also, according to the European Association of Urology and American Urological Association guidelines, RP with extended lymph node dissection, alone or in combination with adjuvant therapies,should be considered as a reasonable treatment option for cancer control outcomes (10). In 1998, D'Amico et.al reported the efficacy of a combination of clinical T stage, preoperative PSA value and biopsy Gleason score (GS) and considered patients with PSA≥20ng/ml or biopsy GS≥8 or clinical T stage ≥2c as high risk patients (11). However, it has been shown to be difficult to predict the clinical outcome in patients with high risk PCa using D'Amico classification before RP because encompasses a heterogenous group of patient. For example, from a clinician point of view it could be difficult to weight the risk beetwen a patient with PSA 20ng/ml, Gleason 4+3, stage T2c disease and another one with PSA 5ng/ml, Gleason 4+4 and stage T1c. Which patient is ideal candidate for RP or radiation therapy and which parameter is most important? With this regards, it is difficult to apreciate the significance of each of these variables

for the prediction of disease progression or recurrence.

Thus, the role of clinical T stage is controversial sincefailed to show a significant correlation with disease reccurence and display a interobserver variablity (12). However, in recent years, modern multiparametric pelvis MRI becomes a useful tool for clinical T stage and clinical decision making regarding definitive treatment and help clinicians to councel their patients about how agrresive is their disease prognosis and the need for adjuvant therapy (13).

In the same way, the biopsy GS was not a significant independent predictor foradverse outcomeinpatients undergoing RP (14).Also, several studies demonstrated that patients with biopsy GS>8 and organ confined disease had a good prognosisafter RP (15). In addition, several authors reported downgrading the biospy GS on final RPspecimen and good biochemical progression free survival or cancer specific mortality (16).

Likewise, PSA it is an important parameter to evaluate clinical outcome since patients with higher PSA have poorer prognosis than those with lower PSA. However, Zwergel et.al and Ngyuen et. al recommended RP as a viable primary treatment option in selected cases of high risk PCa patients wth preoperative PSA >20ng/ml (17,18). Also, data from SEARCH study and Ploussard et al study showed encouraging results regarding the biochemical control and overall survivalafter RP for high risk PCa patients (19,20). Nevertheless, D'Amico et. al criteria for high risk PCa remains largely used and is also adopted by American Urology Association.

Researchers tried to improve the characterization of high-risk patients and created different predictive models by inclusion pre or postoperative variables and/or stratify patients for different outcome such as biochemical reccurence (BR), cancer specific mortality (CSM), extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node involvement (LNI). Accurate risk stratification, both at the time of diagnosis and postsurgery, is esential. In other words, it is important todistinguish patients cured by RP and spared them from the potential impact of adjuvant therapy. Also, patients requires modelstailored to their individual characteristics for accurate predictions of treatment outcomes, both oncologic and functional. For example, for a patient could be more important oncologic outcome and survival benefit and another could consider urinary incontinence or erectile dysfunction unacceptable. Therefore, preoperative and postoperative predictive models using potential predictorsand different endpoints were developed.

Table 1. Predictive models used for the prediction of outcomes in high risk PCa patients

	Study	Pts	Outcome	Parameters
Preoperative				
	Ohori et al.	763	Side-specific ECE	cT,PSA, bGS, ppbc and pcpbcsite specific
	Koh et al	763	SVI	cT, PSA, bGS, % of cancer at the base
	Gallina et al.	666	SVI	cT, PSA, bGS, ppbc
	Baccala et al	6740	SVI	cT, PSA, bGS, age
	Cagiannos et al	5510	LNI	cT, PSA, bGS
	Briganti et al	602	LNI	cT, PSA, bGS
	Kattan et al	983	BR	cT, PSA, primary and secondary bGS
	Stephenson et al	1978	BR	cT, PSA, bGS, No of pbc, year of surgery
	Cooperberg et al	1439	BR	cT, PSA, bGS, ppbc, age
Postoperative				
	Kattan et al	996	BR	PSA, GS, ECE, SVI, LNI, SMS
	Suardi et al	601	BR	pT, GS, SMS, type of surgery, adjuvant RT
	Cooperberg et. al	3837	BR and CSM	PSA, pGS, SM, ECE,SVI,LNI

Based on clinical tumor stage, PSA level and GS, Partin et al. developed in 1997 the well-known look-up table for prediction of organ-confined disease, isolated capsular penetration, SVI or pelvis LNI in a population of 4,133 subjects (21). However, external validation of this predictive tool showed conflicting resultsas shown by other auhors(22,23).

Ohori et al developed in 2004 a nomogram for the prediction of side-specific ECE that can have impact on RP technique (24). The authors showed that the following parameters: prostate cancer in each lobe, cT stage, the highest Gleason sum in any core, percent of positive cores, percent of cancer in the cores from each side and PSAare significant predictors of side-specific ECE. His nomogram achieved an accuracy of 81% and was externally validated by other authors (Steuber et al in 2006 and Zorn et al in 2007) in robotic RP (25,26).

Other authors developed nomograms predicting SVI. Koh et al. (2003)incorporatedserum PSA level, primary Gleason grade, and percent cancerat the base in

his nomogram and demonstrated that biopsy cores from the base significantly predicted SVI (27). On the other hand, Baccala et al. (2007) and Gallina et al. (2007) used for their nomograms percentage of positive biopsy core (ppbc), age, clinical T stage, PSA serum level and biopsy GS (28,29).

Regarding theLNI, the most widely used nomograms were established by Cagiannoset al. (30), and Briganti et al. (31). Pretreatment PSA, clinical stage, biopsyGleason sum and institution were predictors in Cagiannos nomogram (accuracy 76%) while PSA, clinical stage, biopsy Gleason sum and number of lymph nodes removed in Briganti nomogram (accuracy of 83%).

To date, several predictive models before RP weredeveloped for predicting the BR or CSM. Such tools would be helpful to councel patients at the moment of diagnosis of PCa. For example, Kattan et al. developedin 1998 and in 2006nomogramfor prediction of BR after RPat 5 and 10 years respectfully, and included clinical-tumor stage, the serum PSA level and biopsy Gleason scores(32,33).Stephenson et al developed a nomogram for predicting CSM following RP for clinically localized PCaand showed that serum PSA level, biopsy Gleason grade and year of surgery were associated with PCa specific mortality(concordance index was 82%)(34).

Finally, in 2005, Coopenberg et al. developed the University of California San Francisco Cancer of Prostate Risk Assessment (UCSF-CAPRA) score to predict disease recurence after RPby using pre-operative PSA, biopsy GS, clinical T-stage, percentage of positive biopsy cores and age (12). Additionally, the UCSF CAPRA score offers another definition for high risk PCa. Score of 6 up to ten define high risk patients with PCa.

Many authors tried to enhance risk stratification by adding parameters such as the extent of cancer in needle biopsy, PSA velocity, PSA doubling time, or the presence of tertiary gleason pattern. At present,EAU guidelines recommends PHI test that combines total PSA, free PSA and the (-2) pro PSA isoform (p2PSA) for clinical-decision making in men with a PSA between 4-10 ng/ml. However, Mearini et al showed its significance for the detection of agressive PCa (35). The test was approved by FDA in 2012 and is commercially available from Beckman Coulter Diagnostics. It is possible that this test would be used in combination with other markers to improve risk stratification of PCa in the future.

However, pretreatment variables provide only an approximation of cancer severity. An advantage of RP is that it provides a more accurate assesment of GS, pathological tumor stage orsurgical margin status that may improve prognostic accuracy of preoperative models. Also, postoperative predicitive tools aid in determing the need for adjuvant therapy.

In 1999 Kattan et al. developed a post-operative nomogram to predict the 7-year biochemical disease recurrence (36). Kattan nomogram included PSA,final Gleason sum, capsular invasion, surgical margin, invasion of the seminal vesicle and LNI, and provided 89% accuracy.In 2005 Stephenson et al. (37) updated Kattan nomogram for the prediction of bichemicaldisease reccurence to 10 years followingRP. Moreover, Suardi et al. included in his nomogram pathological T stage, GS, surgical margin status, type of surgery and adjuvant radiotherapyandextented the prediction of BR up to 20 years after surgery(38). The model has an accuracy of 77.2–80.6% and wasvalidated by other authors.

PCa is one of the common cancers with a large genetic component as it is demonstrated by increasing risk of developing PCa among first degree relatives or for men with two or more affected relatives. Over the last decade, many studies have tried to adress the unmet clinical need for predicting agressive PCa using gene expression signatures. The Decipher genomic classifier was developed by researchers from Mayo Clinic and GenomeDX Bioscience to predict early metastatic progression after RP(40).Decipher ® is a genomic test for PCathat assesses the activity of 22 RNA markers associated with metastatic disease and has been demonstrated to be independently prognostic of PCa death in a high risk surgical cohort. This assay now commercially available allow physicians and their patients to make adequate informed consent about postoperative care and may enable early indication of adjuvant therapy in high risk patients following RP.

Likewise, Cooperberg and colleagues developed a biopsy-based genomic prostate score as a predictor of high-risk extracapsular PCa (41). The author validated a RT-PCR expression assay of 17 cancer-related genes associated with high grade GS or pT3 disease, using very small biopsy tumor volumes. This assay was developed by Genomic Health Inc. (Redwood City, CA) and is currently commercially available under the trade name Oncotype DX® to help doctors to identify high risk patients and start immediate therapy as an initial management strategy.

The cell cycle progression (CCP) test (Prolaris®) is a novel tissue based prognostic assay that analyzed the expression of 31 cell cycle progression genes, nor-

malized to 15 housekeeper genes. The CCP score was externally validated to have significant prognostic accuracy in predicting cancer specific mortality after RP outcomes. Bishoff et. al validated the prognostic usefulness of the score in the biopsy samples of men treated with RP. This comercially available tool was designed to improve risk stratification and facilitate risk-adapted strategy for patients with clinically localized PCa (42).

There are few post-RP models predicting the risk of PCa-specific mortality: D'Amico et al. nomogram quantifies PCa mortality risk prediction based on PSA velocity and Freedland et al. based on post-RP PSA doubling time. (43,44)

Finally, there are published data on whether surgeon experience can be considered an independent predictor for cancer control or functional outcomes. While Kattan et al. concluded that a nomogram incorporating surgeon experience showed a modest effect to predict the probability of reccurence (45), data from other studies revealed excellent rates of cancer control when a patient with PCa was treated by the most experienced surgeons (46). Additionally, surgeon experience should be considered as a risk predictor for functional outcomes such as urinary incontinence or impotence (46).

Conclusions

To conclude, the reason for the current review regarding the role of predictive toolswas to provide uptodate information that can help physicians in clinical decision making for patients with high risk diseaseat the time of initial diagnosis and after RP.

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