Critical Reviews in Oncology / Hematology 120 (2017) 180–193

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Biomarkers in prostate cancer – Current clinical utility and future perspectives

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ARTICLE INFO

Keywords:
Biomarker
Prostate cancer
Molecular marker
Genetic marker
Prognostic
Predictive

ABSTRACT

Current tendencies in the treatment course of prostate cancer patients increase the need for reliable biomarkers that help in decision-making in a challenging clinical setting. Within the last decade, several novel biomarkers have been introduced. In the following comprehensive review article, we focus on diagnostic (PHI®, 4K score, SelectMDx®, ConfirmMDx®, PCA3, MiPS, ExoDX®, mpMRI) and prognostic (OncotypeDX GPS®, Prolaris®, ProMark®, DNA-ploidy, Decipher®) biomarkers that are in widespread clinical use and are supported by evidence. Hereby, we focus on multiple clinical situations in which innovative biomarkers may guide decision-making in prostate cancer therapy. In addition, we describe novel liquid biopsy approaches (circulating tumor cells, cell-free DNA) that have been described as predictive biomarkers in metastatic castration-resistant prostate cancer and might support an individual patient-centred oncological approach in the nearer future.

1. Introduction

In 2012, over 400,000 men in Europe were newly diagnosed with prostate cancer (PCa) (Ferlay et al., 2015). Although clinical parameters such as prostate specific antigen (PSA) value, imaging diagnostics and histopathological scores (e.g. Gleason score) allow certain risk stratification, they do not allow a definite statement about the individual patient's prognosis (Wang et al., 2014). This might lead to unnecessary treatment on the one hand, but also deny potentially favourable treatment on the other hand, and ultimately harm the patient.

Current tendencies in the urooncological field increase the need for reliable biomarkers that help in decision-making in challenging clinical settings. First, in the PSAera, an increasing number of potentially indolent low-risk prostate carcinomas are being diagnosed (Schroder et al., 2014). According to current European guidelines, various evidence-based treatment options exist for these patients and validated biomarkers to guide the pre-treatment decision process are urgently needed for this increasing patient subgroup (Mottet et al., 2017). In addition, adjuvant treatment options for advanced tumor stages increase and innovative biomarkers might be of great clinical usefulness if they could assist in guidance towards the most beneficial treatment arm.

In the last decade, numerous biomarkers have been introduced. In the following comprehensive review article, we focus on diagnostic, prognostic and predictive biomarkers that are in widespread clinical use and are supported by evidence. Hereby, we focus on multiple clinical situations in which novel biomarkers may guide decision-making. Importantly, these clinical situations are not exclusive and overlaps between the respective biomarkers exist. Lastly, we illustrate novel approaches in precision oncology that might support an individual patient-centred oncological approach in the nearer future.

2. Diagnostic biomarkers

Although the combination of digital-rectal examination and PSA value allows correct PCa risk stratification in the majority of patients, a significant proportion of indeterminate findings leave the treating physician uncertain whether to perform an invasive prostate biopsy or not (Thompson et al., 2004). Thus, innovative diagnostic biomarkers must guide the decision who to biopsy and who to re-biopsy after an initially negative biopsy and continuing suspicion of PCa. The studies discussed in this section are summarized in Table 1.

2.1. Prostate health index PHI® (Beckman Coulter, Brea, USA)

Introduction of the PSA value has somewhat revolutionized the

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https://doi.org/10.1016/j.critrevonc.2017.11.007
Received 2 August 2017; Received in revised form 30 September 2017; Accepted 12 November 2017

Table 1
Summary of studies investigating diagnostic biomarkers that are discussed in the current review article (AUC = area under the curve, BCR = biochemical recurrence, CI = confidence interval, CSS = cancer-specific survival, DRE = digital rectal examination, MiPS = Mi-prostate score, mpMRI = multi parametric MRI, NPV = negative predictive value, OR = odds ratio, PCa = prostate cancer, PHI = prostate health index, tPSA = total prostate specific antigen, %fPSA = percentage of free PSA, PPV = positive predictive value, PV = predictive value, RR = risk ratio, SOC = standard of care).

Study	Biomarker	Study cohort	Endpoints	Main Results
Stephan et al. (2013)	PHI	1362 patients from 4 centers undergoing systematic prostate biopsy (668 patients with PCa, 694 without PCa; tPSA 2–10 ng/ml)	Detection of any PCa	PHI (AUC = 0.74) with better diagnostic performance compared to%p2PSA (AUC = 0.72), p2PSA (AUC = 0.63), %fPSA (AUC = 0.61) and tPSA (AUC = 0.56)/Significantly higher median PHI scores in patients with Gleason ≥7 PCa (Phi = 60 vs. Phi = 53, p = 0.0018)
Tosoian et al. (2017)	PHI	118 patients from 1 center with elevated PSA; (> 2 ng/ml) and negative DRE undergoing prostate biopsy	Detection of clinically significant PCa (Gleason ≥ 7 or Gleason 6 > 2 cores or > 50% of any positive core)	Sensitivity 97.9%, specificity 38.0% for PHI density (threshold 0.43) for clinically significant PCa/Sensitivity 100% for PHI density for Gleason ≥ 7 PCa/AUC for PHI density (0.84) outperforms tPSA (0.52), tPSA density (0.70), %fPSA (0.75), the product of%fPSA and prostate volume (0.79), and PHI (0.76) for detection of clinically significant PCa
Gnanapragasam et al. (2016)	PHI	279 patients from 1 center undergoing mpMRI guided transperineal re-biopsy (negative mpMRIs in 94 patients)	Ability to add value to mpMRI in detection of any PCa and clinically significant PCa (Gleason ≥7)	Addition of PHI to mpMRI leads to improved detection ability of any PCa and clinically significant PCa (AUC 0.71 and 0.75) vs. mpMRI and tPSA alone (AUC 0.64 and 0.69)/NPV 0.97 for PHI + mpMRI for excluding clinically significant PCa (threshold ≥35)
Vickers et al. (2010)	4K score	2914 patients undergoing prostate biopsy due to elevated PSA levels of ≥3 ng/ml (PCa detected in 28%)	Detection of any and high-grade PCa in previously unscreened men with elevated PSA	Addition of%fPSA, intact tPSA, and hK2 improved AUC (0.76 vs. 0.64) compared to a model containing tPSA and age alone (p < 0.001)/Application of 4K panel to 1000 men with elevated tPSA would miss 54 of 177 low-grade PCa and 12 of 100 high-grade PCa
Stattin et al. (2015)	4K score	1423 patients with incident PCa cases from Swedish Cancer Registry (235 with metastatic PCa)	Risk of metastatic PCa for different tPSA levels and a statistical model based on 4K score.	Most metastatic PCa occur in men with tPSA in the top quartile [69% (50yrs), 74% (60yrs)]/Among men with tPSA > 2 ng/ml, 4K score significantly improves prediction of metastatic PCa compared with tPSA alone/50% of patients with tPSA > 2 ng/ml were defined as low-risk by the 4K model and had a ≤1% 15-yrs risk of metastatic PCa
Nordstrom et al. (2015)	PHI/4K score	513 men who underwent initial prostate biopsy due to elevated tPSA levels that ranged between 3 and 15 ng/ml	Detection of any and high-grade (Gleason ≥7) PCa	4K score: AUC 69.0 (any PCa) and 71.8 high-grade (PCa)/PHI: 70.4 and 71.1/Both models outperform a base model consisting of tPSA level and age alone (p < 0.0001 respectively)
Van Neste et al. (2016)	SelectMDx	Training cohort (519 patients) and validation cohort (386 patients) after digital rectal examination (DRE) and prior to prostate biopsy	Detection of clinically significant PCa	Multimodal approach (mRNA signature, tPSA density, previous negative biopsies, tPSA, age, family history) with overall AUC of 0.90 (95% CI 0.85–0.95); mRNA signature, tPSA density and previous negative biopsy as most significant components/Similar AUC if DRE is included as an additional risk factor (0.86, 0.80–0.92)
Hendriks et al. (2017)	SelectMDx	172 patients with mpMRI prior to prostate biopsy	Prediction of mpMRI outcomes	Median SelectMDx score significantly higher in patients with suspicious lesion on mpMRI (p < 0.01)/Prediction of mpMRI outcome: AUC 0.83 (SelectMDx) vs. 0.66 (PSA) vs. 0.65 (PCA3)/Significant correlation between SelectMDx score and final PIRADS grade (p < 0.01)
Stewart et al. (2013)	ConfirmMDx	483 patients after negative initial biopsy and re-biopsy within up to 30 months	Detection of any PCa	NPV of 90% (sensitivity 68%, specificity 64%) of the biomarker panel/Confirmation as an independent predictor for any PCa in multivariate analysis [OR 3.17, 95% CI 1.81–5.53; p < 0.001]
Partin et al. (2014)	ConfirmMDx	350 patients from 5 centers after negative initial biopsy and re-biopsy within up to 24 months	Detection of any PCa	NPV of 88% (95% CI 85–91)/Confirmation as independent predictor for any PCa in multivariate analysis (OR 2.69, 95% CI 1.60–4.51)
Fradet et al. (2004)	PCA3	443 patients undergoing prostate biopsy in 5 centers (21%: tPSA < 4 ng/ml; 55%: tPSA 4–10 ng/ml; 24%: tPSA > 10 ng/ml)	Detection of any PCa	Overall sensitivity: 68% [74% (tPSA < 4 ng/ml); 58% (4–10 ng/ml; 79% (> 10 ng/ml)]/overall specificity 89% [91% (tPSA < 4 ng/ml); 91% (4–10 ng/ml); 80% (> 10 ng/ml)]/PPV 75% vs. 38% for tPSA/NPV: 84% vs. 89% (tPSA cut-off 2.5 ng/ml)

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