Acta Clin Croat (Suppl. 2) 2024; 63:71-76
doi: 10.20471/acc.2024.63.s2.11

Professional Paper

BIOMARKERS AND PERSONALIZED MEDICINE IN PROSTATE CANCER – ADVENT OF PRECISION ONCOLOGY IN (RADIO)THERAPY DECISION-MAKING

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SUMMARY – Therapy decision-making in prostate cancer has traditionally been limited to clinical, histopathological, and radiological variables that does not take into account the varying biology of prostate cancer manifestations. It is well-known that disease stratification tools we use in our clinics every day to customize therapy choices for individual patients with prostate cancer fail to capture and address the wide ranges of observed disease clinical courses. Prostate cancer is characterized by significant intra- and interpatient heterogeneity that makes this disease unique and extremely variable. The advent of affordable next-generation genomic sequencing techniques has allowed the incorporation of these data into clinical research, with enormous potential to aid clinical care in the future. The optimal goal of prostate cancer treatment is to personalize treatment specific to a patient's unique clinic-genomic phenotypes. We may thus potentially avoid overtreatment in patients harboring less aggressive disease and undertreatment in patients harboring more aggressive disease. Currently, we lack that ability if we rely only on clinical stratification tools such as the NCCN model, CAPRA scoring, and D'Amico classification. It may be the case that prostate cancer genomics hold the key to understanding and predicting the response to crucial treatment modalities in prostate cancer: androgen deprivation therapy, radiotherapy, and next-generation androgen pathway inhibition therapy. Currently, there are many open questions about how to use these therapies optimally in individual patients. In this freeform narrative review, we summarize the literature and current clinical practice of biomarkers in prostate cancer, specifically focusing on genomic tests utilized in radiotherapy management and/or adjunctive therapies given with radiotherapy.

Key words: *biomarkers; prostate cancer; risk stratification; genomics; radiotherapy; androgen deprivation therapy*

Introduction

Prostate cancer, the most common urinary tract malignancy, is a major global health problem. One in nine men is expected to develop prostate cancer in his lifetime, with a risk of death of 2%[1]. It is challenging

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to determine the most efficient therapy for a given patient, as oncologists need to determine the treatment with the maximum success rate and the minimum toxicity. The treatment for localized or recurrent prostate cancer is mainly based on risk stratification using clinicopathological markers included in internationally accepted consensus guidelines, such as Gleason score, T stage, prostate-specific antigen (PSA) level analysis, and digital rectal examination (DRE). The Gleason score is a 60-year-old grading system used to evaluate disease and was designed as a pattern recognition tool to identify various patterns of prostate cancer. Over the years, the Gleason score has changed and evolved, but it is still not an adequate prognostic tool. DRE and PSA also have a number of limitations and cannot be used as an accurate risk stratification tool[2]. More recently, tumor stage has been assessed using magnetic resonance imaging (MRI) of the prostate, but MRI also has its drawbacks, especially in less advanced tumor stages. Finally, none of these tools used in the clinic have been developed to optimize prognosis or predict response to treatment. The development of biomarkers for prostate cancer is needed to inform and optimize cancer treatment.

Biomarker development

Carcinogenesis is a genetic process that takes place in previously normal tissue that becomes cancerous. A central principle of molecular biology is that RNA is made from DNA, which leads to protein synthesis, and this process can be quantified. The outcome of this process in prostate cancer is measured by histological Gleason score and by the Prostate Imaging Reporting and Data System (PI-RADS) in radiology. However, because it is part of the phenotype and interpreted by humans, it is susceptible to error and highly subjective. What can be objectively measured, however, is the genotype.

In a paper by Spratt[3] published in 2019, tumor gene expression was analysed in 17967 men with high-risk prostate cancer. Approximately 15-20 gene expression signatures were found. This study also showed a high degree of heterogeneity between patients, although the patients included had high-risk prostate cancer, indicating that some men clearly have a biologically more aggressive disease and some have a more indolent disease[3]. This has been the basis for the development of a variety of different genomic tests, some of which have been reliably validated and used in clinical trials[3]. The three main genomic tests used in the United States are Oncotype, Prolaris, and Dechiper, and they all have different indications for when their use should be considered.

The 17-gene Oncotype DX Genomic Prostate Score (GPS) test has been shown to predict negative pathology and is used as a decision support tool for immediate treatment or active surveillance in men with newly-diagnosed prostate cancer with low or favorable-intermediate risk and has recently been included in the National Comprehensive Cancer Network (NCCN) guidelines[4]. Furthermore, GPS was also evaluated in the Canary Active Surveillance Study Cohort as a potential predictor of outcome, but the independent association of GPS with adverse pathology after initial active surveillance was not statistically significant, nor was there an association with upgrade at surveillance biopsy[5].

The Prolaris test combines the University of California, San Francisco Prostate Cancer Risk Assessment (CAPRA) and the molecular assessment of cell cycle progression (CCP) to form the Clinical Cell Cycle Risk (CCR) score. In 2022, Jonathan Tward et al. published a retrospective, multi-institutional study that included intermediate-, high-, and very high-risk prostate cancer[6]. The aim of this study was to assess the ability of the CCR score to predict the risk of metastasis in men receiving radiotherapy with or without androgen deprivation therapy (ADT)[6]. The study showed that the CCR score accurately predicted metastasis and provided clinically useful information with respect to NCCN-recommended risk-based therapies in men receiving radiotherapy, with or without ADT[6]. The benefit of using the CCR score in localized prostate cancer is still unproven.

The third test is Decipher genomic classifier (GC), which has been tested in a number of randomized trials and has consistently improved the prediction of a number of endpoints[7]. A meta-analysis including 42 different studies and 30000 men, both retrospective cohort studies from centers and prospective registries and surveys, evaluated the use of GC[7]. Tissues from biopsies and surgical procedures were used. In all studies, GC was independently prognostic for all study endpoints (adverse pathology, biochemical failure, metastasis, and cancer-specific and overall

survival)[7]. The utility of GC is greatest for intermediate-risk PCa and for decision-making after prostatectomy[7]. Clinical genomic risk groups were created based on these results, combining the NCCN and Decipher risk groups to create a new risk grouping system that improves risk stratification in patients with prostate cancer[8]. The new NCCN clinical-genomic model reclassifies 67% of patients and more accurately classifies them according to their risk, especially in favorable-intermediate risk patients, which can consequently change their treatment plan.

The clinical utility of the genomic test has been demonstrated in several studies, one of which was conducted at the University of California in San Francisco between 2000 and 2016[9]. The men included were under active surveillance, and the aim of the study was to analyze which were the strongest predictors of reclassification of men on surveillance biopsies. The results showed that a high genomic score was associated with reclassification within three years after the start of active surveillance[9].

The Decipher gene test was also evaluated in a multi-institutional study involving more than 850 men, conducted by Vince Jr et al. and published in 2022. This study included 264 patients on active surveillance and 454 patients who received radical treatment. The results showed that the high-risk Decipher biopsy result was strongly and independently associated with switch from active to definitive treatment in the active surveillance group and treatment failure in patients who received radical treatment[10].

These results raise the question of whether men with high-risk Decipher test results should be actively monitored.

Spratt presented a study at the ASCO GU 2022 conference in which tumor samples from the NRG/RTOG 0126 study were analysed. This study was conducted among men with intermediate-risk prostate cancer who were randomized to different fractionation schedules without the use of concomitant hormone therapy. RNA was extracted from tumor samples, and, after quality control, processed with a Decipher genomic classifier. After obtaining the GC data, the data were correlated with clinical outcomes to assess the prognostic performance of the Decipher test. The results showed that Decipher GC was an independent predictive factor for disease progression, biochemical failure, distant metastasis, and prostate cancer mortality. In addition, the classification of Decipher GC scores into low- and intermediate-risk groups demonstrated clinically meaningful discrepancies in almost all outcome indicators. In addition, the authors found evidence of predictive ability specific to GC with a greater benefit from an increase in radiotherapy dose in patients with higher GC scores.

Furthermore, the GC test was also evaluated in a study conducted by Nguyen et al., published in 2021. In this study, tissue samples from NRG/RTOG 9202, 9413, and 9902 phase III randomized trials (the men included had high-risk prostate cancer) were secured and then analyzed, and GC scores were obtained. The results of this study showed an independent association of GC score with distant metastases, prostate cancer mortality, and overall survival[11]. It also showed significant differences in GC scores in patients with high-risk prostate cancer, suggesting that high-risk prostate cancer is a complex and heterogeneous condition and that GC can help optimize risk stratification and customize shared decision-making[11].

Another study that proved the value of Decipher GC was conducted by Feng et al.[12]. In this study, GC was tested on radical prostatectomy samples from the NRG/RTOG 9601 phase 3 randomized clinical trial conducted between 1998 and 2003. The primary objective of this study was to determine the independent prognostic value of GC for distant metastases, while the secondary objectives were prostate cancer mortality and overall survival. In this study, the GC test was prognostic for distant metastases, prostate cancer mortality, and overall survival[12]. In addition, this study inadvertently showed that hormone treatment did not benefit men with lower GC scores as much as men with higher GC scores. It also showed that in patients who received early salvage radiotherapy, those with higher GC scores achieved an 11.2% improvement in 12-year distant metastases and a 4.6% improvement in overall survival as a result of additional hormone therapy[12].

Prospective randomized trials using Decipher GC

These results have evolved into two very large randomized phase 3 studies: Guidance and Predict RT. The Guidance study enrolled men with mostly intermediate-risk adverse disease. In this study, the Decipher GC test will be used to try to determine whether the enrolled patients will benefit from hor-

mone therapy or will be able to receive radiotherapy alone. For men with high-risk disease who are often treated with radiation and long-term hormone therapy, GC will determine whether hormone therapy can be shortened in the case of a lower genomic score or whether it should be amplified with a newer anti-androgen drug called darolutamide to improve their outcomes.

The second phase 3 study is called Predict RT. Once again, the investigators will use the Decipher GC test to divide patients into high- and low-genetic risk groups. The low gene risk group will be randomized to receive standard radiotherapy and hormone therapy or less intensive hormone therapy and radiotherapy. The high genetic risk group will be treated either with standard radiotherapy and 2 years of hormone therapy or with more intensive treatment with the addition of apalutamide to the standard treatment.

Artificial intelligence in prostate cancer therapy personalization

Another prostate cancer personalization tool has been revealed in an article published in 2022 by Esteva et al.[13]. The authors presented the individualization of prostate cancer treatment by prognosticating long-term, clinically relevant outcomes by means of a multimodal deep learning architecture and learning models using clinical data and digital histopathology from prostate biopsies[13]. The models were trained on the basis of five multi-institutional randomized phase III trials, clinical data, and a dataset of 16204 histopathological slides to predict the risk of various oncological outcomes (5- and 10-year biochemical failure, distant metastasis, prostate cancer-specific and overall mortalities). This artificial intelligence-based tool offers improved prediction compared to NCCN risk groups and helps oncologists estimate the most likely outcomes for specific patients and optimize treatment by using computerized predictors. This could enable worldwide access to personalized treatment, as every clinic could offer such options by using digital scanners and having access to the Internet[13].

Predictive biomarkers

Prostate cancer has a very quiescent mutational environment, especially in the localized stage. There are currently no predictive tools that would guide the use of radiotherapy. Radiosensitivity index is a gene expression test that could potentially help us determine which patient will benefit from radiation therapy[14]. Unfortunately, so far we have very limited and not significant data on its use in prostate cancer.

A study published in 2016 by Zhao et al. aimed to develop a gene expression signature that would help us determine which patients will benefit most from post-operative radiotherapy. They developed the Post-Operative Radiation Therapy Outcomes Score (PORTOS), which contains 24 genes. Their results showed that patients with a high PORTOS score who underwent postoperative radiotherapy were less likely to have distant metastases at 10 years than those who did not undergo radiotherapy[15]. However, the authors agree that, given that this tool has only been used in one retrospective study, more data are needed to draw further conclusions about the predictive power of PORTOS[15].

Spratt presented the first predictive biomarker for the benefit of androgen deprivation therapy in localized prostate cancer at the ASCO GU 2022 conference. The investigators used digitized pre-treatment biopsies from five randomized phase III NRG Oncology trials involving men receiving radiotherapy with or without androgen deprivation therapy. Four training sets from the NRG/RTOG trials were used to develop an AI model and a predictive biomarker derived from it. The resulting AI model was validated in the NRG/RTOG 9408 trial. Patients with a positive biomarker had 10% less distant metastatic disease 15 years after treatment. Men with biomarker-negative disease (almost two-thirds of men in the trial) did not benefit from additional hormone therapy, demonstrating that most patients treated with radiotherapy in the NRG/RTOG 9408 trial did not need androgen deprivation therapy.

Conclusion

Almost all decisions about prostate cancer treatment are based on prognosis. Current standard risk stratification tools are insufficient, leading to errors in disease assessment and treatment. Improved clinical tools designed to improve risk stratification exist but are rarely used. Gene expression tests have even been shown to be superior to these clinical tools, but their global application faces many challenges, mainly due to their financial burden, but also due to unequal validation.

Artificial intelligence offers a new, exciting, and affordable tool that can help us predict outcomes in men with localized prostate cancer treated with curative intent using common radiotherapy±androgen deprivation therapy modalities.

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Sažetak

BIOMARKERI I PERSONALIZIRANA MEDICINA U RAKU PROSTATE - POJAVA PRECIZNE ONKOLOGIJE U DONOŠENJU ODLUKA O (RADIO)TERAPIJI

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SAŽETAK: Odlučivanje o liječenju raka prostate tradicionalno se temelji na kliničkim, hiostološkim i radiološkim podacima koji ne uzimaju u obzir promijenjivu i raznoliku biologiju raka prostate. Poznata je činjenica da stratifikacijski modeli koje svakodnevno koristimo u kliničkoj praksi ne mogu predvidjeti raznolike kliničke ishode bolesti koje redovito opažamo. Rak prostate karakterizira značajna heterogenost, što čini ovu bolest jedinstvenom i vrlo varijabilnom. Dolazak cjenovno pristupačnih novih tehnika sekvencioniranja genoma donosi veliki potencijal za istraživanje i kliničku primjenu u budućnosti. Optimalni cilj liječenja raka prostate je personalizirati liječenje na osnovi bolesnikovih kliničko-genomskih osobina. Ako to ostvarimo, u teoriji možemo izbjeći nepotrebno liječenje u bolesnika koji imaju indolentniju bolest i nedovoljno liječenje u onih bolesnika koji imaju agresivniju bolest. Trenutno takve mogućnosti nam ne pružaju klinički alati koje koristimo svaki dan, kao npr. NCCN, CAPRA ili D'Amico klasifikacija. Vrlo vjerojatno genomika drži ključ odgovora na liječenje raka prostate poznatim modalitetima kao što je androgena deprivacijska terapija, radioterapija ili terapija novom generacijom inhibitora androgene osovine. Trenutno postoje brojne nedoumice kako optimalno koristiti ove opcije liječenja u pojedinog bolesnika. U ovom preglednom članku napravili smo pregled literature i trenutne kliničke prakse u području biomarkera u raku prostate, fokusirajući se naročito na genomske testove koji su razvijeni primarno prema bolesnicima koji se liječe radioterapijom, sa ili bez dodatne hormonske terapije.

Ključne riječi: *biomarkeri, rak prostate, stratifikacija rizika, genomika, radioterapija, androgena deprivacijska terapija*