Acta Clin Croat (Suppl. 3) 2022; 61:86-91
doi: 10.20471/acc.2022.61.s3.13

Professional Paper

GENOMICS OF PROSTATE CANCER: CLINICAL UTILITY AND CHALLENGES

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SUMMARY: The studying of prostate cancer genomics is important for understanding prostate cancer biology, it can provide clinically relevant stratification into subtypes, the development of new prognostic and predictive markers in the context of precision medicine, and the development of new targeted therapies. Recent studies have provided detailed insight into genomics, epigenomics and proteomics of prostate cancer, both primary and metastatic castration-resistant (mCRPC). Many mutations have been discovered, both those that occur early in the carcinogenesis and progression as well as those responsible for the resistance to therapy occurring later under the influence of treatment. A large number of characteristic mutated signaling pathways has been identified, e.g. the mutations in DNA repair pathway were found in 23% of mCRPC, which suggests potential response to PARP inhibitors. Multifocality and intralesional genomic heterogeneity of prostate cancer make the clinical application of genomics complicated. Although a great progress was made in understanding prostate cancer genomic, and clinical studies related to its routine application are ongoing, prostate cancer genomics still needs to find its standard wide routine application in patients with prostate cancer.

Key words: *Prostate Cancer; Genomics; Tumor Biomarkers; Genetic Heterogeneity*

Introduction

Prostate cancer is the second most common cancer in men, with an estimated 1,414,259 new cases and 375,304 deaths worldwide in 2020 (1). The patients with localized prostate cancer are successfully treated with surgery and radiotherapy. For patients with metastatic prostate cancer, androgen deprivation therapy is the standard treatment. However, most of these patients experience the progression to metastatic castration resistant prostate cancer (mCRPC) and eventually die after progression (2). Studying and understanding prostate cancer genomics could provide, in addition to better understanding of prostate cancer biology, also the development of new prognostic and predictive markers and patient-tailored treatments that would result in improved patient outcomes.

The development and current wide availability of next-generation sequencing (NGS) allow for precise mapping of genomic, transcriptomic and epigenomic alterations in cancer samples taken from patients (3). One of the challenges is the interpretation of large amount of data generated by whole-genome or whole-exome sequencing. These challenges are successfully met by advanced bioinformatics tools which,

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in addition to interpreting genomic data, also make it possible to integrate genomic with proteomic and clinical data related to patients. Although there are still certain challenges involved in integrating genomic analysis into routine medical care for cancer patients, genomic analyses, mostly targeted NGS panels are already communicating the clinical decisions regarding treatment for many cancer patients. In addition to identifying targetable mutations for targeted therapies in the era of precision medicine, NGS approaches could also improve the selection of patients for immunotherapy with immune checkpoint inhibitors (ICI) because many studies have shown tumor mutational burden determined by NGS to be a valuable predictive marker for immune checkpoint inhibitor (ICI) therapy (4,5). Although ICI therapy has shown limited efficiency for prostate cancer, one study has shown that prostate cancer patients with high tumor mutational burden had better overall survival compared to prostate cancer patients with low tumor mutational burden (6-8).

Genomic landscape of prostate cancer

Even before the occurrence of NGS studies, several characteristic recurring genetic alterations in prostate cancer were identified. These include mutations in *TP53* tumor-suppressor gene, loss of tumor-suppressor gene *RB1*, mutations and amplifications of *AR* (androgen receptor) gene, inactivating mutations in *PTEN* (phosphatese and tensin homolog) gene, amplifications of *MYC* gene, *TMPRSS2-ERG* gene fusions, and others (9,10).

Extensive NGS-based genomic, transcriptomic, and epigenomic studies of prostate cancer have provided much deeper understanding of prostate cancer genomics including stratification into molecular subtypes with potential clinical relevance. In a large study performed as a part of The Cancer Genome Atlas (TCGA) project, there were 333 primary prostate carcinomas studied on genomic, transcriptomic and epigenomic level (11). This study identified 13 significantly mutated genes, with some of them (*BRAF*, *HRAS*, *AKT1*, *CTNNB1*, *ATM)* not previously identified. The important result of this study is a molecular classification of primary prostate carcinoma into seven subtypes defined by specific gene fusions (*ERG*, *ETV1*, *ETV4*, *FLI1*) or mutations (*SPOP*, *FOXA1*, *IDH1*). There were also some potentially targetable mutations identified including mutations in genes involved in DNA repair pathways making patients with these mutations the possible candidates for PARP inhibitor therapy (12).

Primary prostate cancer often has a good prognosis related to indolent course of the disease. The greatest challenge is the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) with overall poor prognosis. It was shown, as expected, that genomic profile in mCRPC differs from the one in localized primary prostate cancer (13). In a large study involving 150 patients with mCRPC, there was a whole exome and transcriptome sequencing performed. Driver genomic aberration was found in nearly all of the samples with most frequent mutations in *AR* (androgen receptor) gene found in 63% of patients, *ETS* gene fusions in 57% of patients, *TP53* gene in 53% of patients, and *PTEN* gene in 41% of patients (13). The comparison of the results from this study with the studies researching the primary prostate cancer has shown that several mutations were significantly enriched in mCRPC, with mutation in *TP53* gene being the most selectively mutated in mCRPC, and the mutation in *AR* gene being found exclusively in mCRPC (12-14). Among 150 patients with mCRPC, 89% had clinically actionable genomic aberration, most frequent being in AR signaling pathway (71% of patients), PI3K signaling pathway (49% of patients), Wnt signaling pathway (18% of patients), and DNA repair pathways (23% of patients) (13).

In addition to confirming the importance of previously known genomic aberrations in prostate cancer, the genomic studies have also reported new significant mutations. Such mutations are inactivating mutations in *SPOP* gene coding for speckle-type POZ protein found in around 10% of both primary and metastatic prostate cancers (15). The mutations in *SPOP* gene are driver mutations in prostate cancer carcinogenesis. The proposed mechanism used by these mutations to drive carcinogenesis involves the deregulation of both PIK3/mTOR and AR signaling pathways (16). Genomic profiling studies have shown that prostate cancer patients with *SPOP* mutations have a new molecular subtype of prostate cancer with distinguishing genomic and epigenomic profile (11,14). Several studies have shown potential clinical significance of *SPOP* mutations in patients with prostate cancer as a favorable prognostic and predictive marker. Patients with mCRPC harboring *SPOP* mutations had a significantly better response to therapy with abiraterone

(17). In another study involving the patients with *de novo* metastatic castration-sensitive prostate cancer who receive standard androgen deprivation therapy with the presence of *SPOP* mutations was associated with significantly longer median progression-free survival and overall survival (18).

Clinical utility of prostate cancer genomics

Genomic profiling is currently not used extensively as a routine part of prostate cancer diagnostic and treatment protocols. However, several genomic profiling studies put forward several genomic alterations with potential clinical utility as prognostic or predictive markers.

Mateo et al. performed whole-genome sequencing on 470 patients with primary prostate cancer before therapy. In 61 of these patients, an additional biopsy was sequenced after the development of mCRPC. They reported no gene in primary cancer being associated with the time of progression during the androgen deprivation therapy, while only the mutations in *RB1* gene were associated with shorter survival (19). The comparison of primary cancer with later mCRPC in the same patients revealed significantly higher rate of mutations in *AR*, *RB1*, *TP53* and genes of PI3K/AKT signaling pathway in mCRPC (19). In another study where whole-genome and transcriptome sequencing was performed in 101 patients with mCRPC, the mutations in *RB1* gene were significantly associated with shorter overall survival (20). The same study showed that the resistance to enzalutamide therapy was associated with increased activity of Wnt/β-catenin signaling pathway and with mutations in *CTNNB1* gene coding for β-catenin (20). Abida et al. studied 429 patients with mCRPC by sequencing whole-exome and transcriptome, out of which, 128 patients were receiving the first-line therapy with abiraterone or enzalutamide. They reported only the mutations in *RB1* gene being associated with shorter overall survival, and the mutations in *RB1*, *TP53* and *AR* genes being associated with shorter time needed to change the treatment in patients treated with abiraterone or enzalutamide (21). In the study by Deek et al., the patients with metastatic castration sensitive prostate cancer were studied using commercial targeted cancer NGS panels showing the connection of mutations in *TP53* gene with significantly shorter radiographic-progression free survival and shorter time needed for the development of castration resistance (22). In this study, the mutations in *TP53* gene and in genes involved in DNA double-strand brake repair were associated with higher number of metastases (22).

In addition to the development of new better prognostic markers in patients with prostate cancer, genomic and transcriptomic studies have potential in personalized therapy. In one of the studies, there was a Decipher Genomic Classifier (GC), a commercial transcriptomic test that analyses expression of 22 genes and has already shown prognostic value in predicting the development of metastases after radical prostatectomy, studied as a predictive marker for the therapy with bicalutamide (23). When analyzed in patients from phase III randomized clinical trial where patients received salvage radiotherapy with either placebo or bicalutamide, Decipher GC score was used as an independent prognostic predictor in all patients and could predict the effect of bicalutamide on overall survival making it potentially useful predictive marker for personalized therapy (24).

Prostate cancer genomic heterogeneity

One of the major challenges in accurate routine use of genomic profiling in cancer is genomic heterogeneity. Due to the mechanisms of clonal evolution and cancer genomic instability, new clones appear during cancer progression, and different subclones can initiate different metastases of the same primary cancer (25,26). This mechanism is particularly relevant for secondary acquired resistance to therapy by accumulating additional mutations. Genomic heterogeneity of cancer manifests itself as intralesional or intralesional heterogeneity. Intralesional heterogeneity arises due to the presence of genetically different clones in the same cancer lesion, while intralesional heterogeneity refers to genetic differences between different cancer lesions (primary cancer and different metastases) in the same patient. Genomic heterogeneity represents a challenge in making treatment decisions based on genomic profiling in the context of precision medicine because genomic profile of an analyzed sample lesion (eg. primary cancer biopsy) might not be relevant for other lesions (eg. metachronous metastasis).

Prostate cancer shows different types of genomic heterogeneity. The distinguishing characteristic of prostate cancer is the multifocality of primary prostate cancer. More than 80% of prostate glands with cancer have more than one topographically distinct foci of cancer (27). Genomic profiling studies have shown

that different prostate cancer foci in the same patient have distinct non-overlapping genomic profiles including differences in cancer driver gene mutations (28). The studies of DNA methylation patterns have also shown clear epigenomic differences between different foci of prostate cancer (29,30). Genomic heterogeneity of different foci in the case of multifocal prostate cancer represents a challenge in the routine use of genomic profiling for driving treatment decisions in patients with prostate cancer. This is corroborated by a case report that has shown that genomically different foci of prostate cancer in the same patient have significantly different response to androgen deprivation therapy (31).

The pertinent question related to clinical utility of genomic profiling in the context of prostate cancer genomic heterogeneity is whether different metastases in the same patient are of monoclonal or polyclonal origin. Several studies analyzing different metastases in the same patient on genomic, epigenomic and transcriptomic level have shown high level of conformity regarding driver alterations suggesting monoclonal origin of metastases (32,33). However, some more advanced studies have shown a complex clonal evolution of prostate cancer progression and metastatic spread (34,35). A hypothesis of clonal convergence could explain the observed decreased genomic heterogeneity in more advanced, more aggressive later stage prostate cancer (36).

Genomic profiling of liquid biopsy samples collected from patients with prostate cancer is a promising approach that might overcome several challenges in clinical utility of prostate cancer genomic profiling, particularly the ones related to genomic heterogeneity and clonal evolution. It was shown that the whole-genome sequencing can detect clinically relevant genomic alterations in liquid biopsy samples taken from patients with metastatic prostate cancer (37). Prognostic and predictive value of genomic alterations detected in liquid biopsy samples of patients with prostate cancer, particularly androgen receptor pathway genomic alterations associated with resistance to androgen deprivation therapy, was shown in several studies (38).

Conclusion

Extensive studies analyzing genomic, epigenomic and transcriptomic profiles of prostate cancer have provided better understanding of prostate cancer biology, progression and resistance to therapy. Genomic alterations with potential clinical utility (e.g., *RB1* mutations associated with worse prognosis, and *SPOP* mutations associated with better prognosis) have emerged from these studies. The knowledge acquired by studying prostate cancer on whole-genome, transcriptome and epigenome level has confirmed that prostate cancer is a complex heterogeneous disease that evolves over time and under selective pressure of therapy which challenges the profiling of prostate cancer needed for predicting the treatment in the context of precision medicine.

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Sažetak

GENOMIKA RAKA PROSTATE: KLINIČKA PRIMJENA I IZAZOVI

I. Šamija i *A. Fröbe*

Istraživanje genomike raka prostate je važno za razumijevanje biologije raka prostate, može omogućiti klinički relevantnu stratifikaciju u podtipove, razvoj novih prognostičkih i prediktivnih biljega u kontekstu precizne medicine i razvoj novih ciljanih terapija. Novija istraživanja omogućila su detaljan uvid u genomiku, epigenomiku i proteomiku raka prostate, i primarnog i metastatskog otpornog na kastraciju (mCRPC). Tako je otkriven velik broj karakterističnih mutacija, kako onih koje se događaju rano u nastanku i progresiji raka prostate, tako i onih koje nastaju kasnije pod utjecajem terapije i odgovorne su za rezistenciju na liječenje. Identificirani su signalni putovi karakteristično pogođeni mutacijama, npr. u 23% mCRPC nađene su mutacije u genima za popravak oštećenja DNA što ukazuje na moguć odgovor na liječenje PARP inhibitorima. Ono što komplicira kliničku primjenu genomike je multifokalnost te intralezijska i interlezijska genomska heterogenost raka prostate. Iako je ostvaren veliki napredak u razumijevanju genomike raka prostate i provode se klinička istraživanja vezana uz njenu rutinsku primjenu, genomika još treba naći svoju standardnu široku rutinsku primjenu u bolesnika s rakom prostate.

Ključne riječi: *rak prostate; genomika; tumorski biljezi; genetska heterogenost*