



Localized prostate cancer genotyping: another step towards personalized therapy

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Prostate cancer (PCa) is marked by a broad heterogeneous spectrum of clinical behavior, ranging from indolent subclinical forms up to aggressive metastatic and rapidly lethal tumors. This complex landscape of PCa behavior denotes the extreme genomic heterogeneity of this tumor type (1). Interestingly, the genomic heterogeneity of PCa is observed not only between the primary (localized) tumor and the advanced (metastatic) tumor samples, but also within each of the two disease stages. Certainly, PCa molecular characterization could provide an important impact in defining the patients' prognosis and guiding therapeutic decisions. In this light, a pivotal contribution in understanding localized PCa molecular taxonomy comes from the whole exome sequencing molecular analysis of more than 300 primary PCa performed by the Cancer Genome Atlas (TCGA) study group (2). This analysis confirmed the androgenic dependence of primary PCa, the significant incidence (about a quarter) of activating mutations of the phosphoinositide 3-kinase (PI3K)/Akt/mTOR and MAPK signaling pathways, and the possibility to classify the vast majority of PCa tumors into seven subtypes defined by specific gene fusions (ERG, ETV1/4, and FLI1) or recurrent mutations in specific genes (SPOP, FOXA1, and IDH1) (2).

Treatment plans personalization based on genomic classification although promising is still highly unripe. In addition, a further complication of this scenario lies in the vast inter- and intra-tumor genetic heterogeneity. In particular, when considering a radical prostatectomy specimen, multiple different intraprostatic neoplastic

foci can significantly differ in their genomic profile and therefore in biological aggressiveness (3,4). The highly genomic heterogeneity of multifocal PCa tumors, the possible co-existence of PCa foci of independent clonal origin, and the subsequent diverse tumor evolution of each PCa lesion greatly complicate the management of localized PCa. Therefore, PCa risk stratification and the consequent treatment algorithm cannot rely exclusively on limited sampling of the prostate.

Wei *et al.* (5) presented the results of a comprehensive genomic analysis using whole-exome sequencing, single-nucleotide polymorphism arrays, and RNA sequencing performed on multiple non-microscopic and noncontiguous PCa foci in radical prostatectomy specimens derived from four patients with clinically localized National Comprehensive Cancer Network intermediate- or high-risk PCa who did not receive neoadjuvant therapy. DNA and RNA were extracted from three independent tissue cores of the index lesion (based on size) and from one core obtained from all additional spatially distinct tumor foci. The aim of this analysis was to create a genomic fingerprint for each PCa lesion within each prostate gland in order to delineate genomic heterogeneity within the index PCa lesion (intratumoral heterogeneity) and between the different PCa foci (intertumoral heterogeneity). According to the results of previous studies, this analysis confirms the significant intratumoral and intertumoral heterogeneity in somatic DNA alterations between different tumor foci within the prostate gland, thus emphasizing the need and the complexity to identify that specific aggressive

focus responsible of tumor recurrence and/or metastatic spread.

In addition, the important contribution of Wei and colleagues depends particularly on the demonstration that:

- (I) The majority of DNA-derived genomic heterogeneity is conserved at the RNA level, and the combined assessment of both DNA variants and RNA expression has been shown to be more powerful at differentiating subgroups of PCa than either alone. Additional variability in gene expression and gene fusions has been identified when analyzing RNA;
- (II) The bulk of PCa foci analyzed could not be classified as belonging to any of the seven subgroups of the TCGA molecular taxonomic system (2). Accordingly, same results derive from an extended analysis that includes additional 163 tumor foci from 60 men from four public studies; The lack of a correlation with the TCGA taxonomy underlines the importance of further deepening the current knowledge on PCa molecular characterization, stresses the limitations of the classification tools available, and supports the need of novel more reproducible molecular clustering;
- (III) Considerable intratumoral and intertumoral heterogeneity has been also observed between the scores of different commercially available genetic prognosticators, which quantitate for each PCa focus the expression of gene signatures able to stratify indolent versus aggressive tumors: the Decipher (a 22 genes set that estimates the probability of metastatic disease), Prolaris (31 cell-cycle progression genes indicating PCa aggressiveness), and Oncotype DX (12 genes predicting PCa recurrence after surgery). Prospective, systematic analyses of large cohorts of PCa specimens are required to verify if taking into account the range rather than the absolute value of these scores, the average score from two or more intraprostatic PCa foci, cooperativity between scores from different assays on the same tissues, and inclusion of DNA-based data may improve the performance of current prognostic risk tools;
- (IV) The androgen receptor (AR) activity, assessed for each PCa lesion by measuring the expression of a select set of 20 AR target genes, is remarkably diverse both within and among PCa specimens. AR activity does not correlate with any other scores or with the prostate region from which the cores were

obtained, but correlates with Gleason score. Albeit with the limitation of the specific AR-dependent gene set analyzed, the heterogeneity of AR activity raises the question of a possible molecular selection for guiding the androgen deprivation adjuvant therapy indication.

Beyond the fundamental contribution that this study brings in the perspective of a molecular stratification of PCa, several limitations should be taken into account:

- (I) The small sample size of only four PCa patients analyzed. Although this study has extracted the highest number of samples from each prostate gland—between five and seven from each prostate—with each sample highly representative of neoplastic tissue, a larger cohort is strongly suggested to validate and better delineate the hypothesis of multifocal PCa genomic heterogeneity (6);
- (II) The clinically restricted PCa patients (at high-risk of relapse) selected for molecular characterization. PCa molecular profiling should help clinicians in the management of the most critical clinical situations where treatment decisions are not unequivocally accepted.

It means, for instance, in low-risk apparently indolent PCa where active surveillance represents a possible therapeutic option to consider together with active locoregional treatments. Do we think that mapping genetically biopsy specimens may contribute substantially in treatment decisions? The identification of a PCa focus (although not in the index lesion) with aggressive molecular properties could prompt the clinician to an active treatment? Similarly, the genomic characterization of an intermediate or high risk PCa will give substantially information about the selection of patients who will benefit most from adjuvant hormonal therapy (taking into account the heterogeneity of AR activity)?

Moreover, considering that single tumor-biopsy specimen reveals a minority of genetic aberrations that are present in an entire tumor, the problem of adequate sampling of the prostate remains.

In addition, this study lacks a correlation between the genomic profile of the PCa primary tumor and that of cancer cells responsible for relapse/progression/metastasis. It would be very fascinating to being able to identify the aggressive PCa subclone both in the primary tumor and in the metastatic sites, or—even more interesting—in an earlier disease stage through DNA analysis of circulating tumor cells, and to characterize the genomic differences

at different disease stages. An indirect comparison of the key aberrations observed in localized versus advanced PCa revealed that: (I) metastatic castration resistant PCa (mCRPC) has a higher mutational load (more copy-number alterations and mutations); (II) AR signaling, TP53, and PI3K pathway are more commonly mutated in mCRPC compared to primary PCa; (III) no genes are selectively mutated in primary PCa (2,7).

Can we assume in the future to draw an integrated prognostic model that includes biochemical data [prostate-specific antigen (PSA) levels], radiological findings (staging, disease extension), histological features (Gleason Score), clinical parameters and molecular characteristics of the tumor? Such a model should be seen as a dynamic system that periodically guides clinicians to the best therapeutic strategy during the course of the patients' clinical history. Tumor progression is a multistep process that reflects the progressive accumulation of genetic mutations, which confer a selective advantage to cancer cells proliferation. Therefore, the best prognostic model should provide an inherent dynamism and reproducibility at different stages of PCa disease.

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