



# The evolving role of molecular profiling in prostate cancer: basal and luminal subtyping transcends tissue of origin

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Prostate cancer is the second most common cancer in men worldwide, accounting for 15% (1.1 million) of the total new male cancer cases and 6.6% (307,000) of the total cancer deaths in men (1). In the U.S., 161,360 new cases and 26,730 deaths from prostate cancer are estimated for 2017 (2).

The management of localized prostate cancer is guided by clinical and pathologic criteria including stage, grade, and serum prostate specific antigen (PSA) levels (3). Based on these criteria, men with non-metastatic prostate cancer were stratified into three broad and clinically heterogeneous risk categories (4). Over the ensuing decades, algorithmic treatment schemas emerged from prospective clinical trials based on this clinicopathologic risk stratification system (5) and formed the current basis for management decision making (6).

Some of the earliest studies in gene expression profiling of prostate cancer demonstrated distinct taxonomies that were associated with more aggressive forms of the disease (7). However, the clinical translation of these findings has remained largely unrealized. In contrast, breast cancer taxonomies have been more effectively utilized for clinical decision making. This was largely based on the seminal work of Sørlie and Perou (8). Subsequent years saw the development of expression based biomarkers to estimate the risk of breast cancer recurrence in women with early stage disease and to select patients who may benefit from endocrine therapy or chemotherapy (9).

Molecular profiling of prostate cancer has more recently emerged as a reliable method for predictive modeling and clinical risk stratification (10). Indeed recent retrospective data suggest gene expression based classifiers

may outperform traditional clinicopathologic criteria for selecting men with a diagnosis of prostate cancer for active surveillance (11) or men with adverse pathology following prostatectomy for adjuvant radiotherapy (12,13). Given the wide spectrum of prognosis and the myriad therapeutic options available to patients with prostate cancer, a significant unmet need persists for the development and analytic validation of predictive biomarkers.

## Basal and luminal subtyping in prostate cancer

In 2009, Parker and colleagues described the PAM50 classifier in breast cancer, which separated tumors into four distinct classes: luminal A, luminal B, basal and amplified human epidermal growth factor receptor 2 (HER2) (14,15). PAM50 subsequently gained U.S. Food and Drug Administration clearance as a tool for risk stratification in breast cancer. Prostate cancer bears similarities to breast cancer in that both are driven by gonadal hormones and endocrine therapy can be highly effective in both diseases. In this context, Zhao and colleagues explored whether the basal/luminal classification might therefore also be relevant in prostate cancer (16).

In their study, Zhao *et al.* applied the PAM50 classifier across gene expression data, generated using a commercially available array based clinical assay (GenomeDX, San Diego, CA), from 3,782 archived radical prostatectomy specimens. These specimens were derived from six institutional retrospective cohorts and one prospectively collected cohort. They excluded the HER2 subtype from their analysis, noting that HER2 is not amplified in prostate

cancer as it is in breast cancer. They found that the 1,576 retrospectively analyzed prostate tumors clustered in nearly equal proportions across the three remaining subtypes: luminal A (34.3%), luminal B (28.5%) and basal (37.1%). These proportions were conserved in 2,215 expression profiles from prospectively collected prostatectomy specimens in the Genome DX Decipher GRID post prostatectomy cohort.

In their retrospective cohorts, for which follow-up data were available, the authors investigated the prognostic significance of PAM50 clustering. Patients with luminal B tumors were found to have consistently worse outcomes for all clinical endpoints examined, including biochemical recurrence free survival (bRFS), distant metastasis free survival (DMFS), prostate cancer specific survival (PCSS), and overall survival (OS). This contrasts with breast cancer where basal like expression confers a poor prognosis. The PAM50 proliferation score (a composite of proliferative gene expression in the PAM50 cluster) was highest for the luminal B subtype, in line with the relatively more aggressive clinical behavior of this subset. The luminal B subtype was similarly associated with adverse clinical and pathologic characteristics including higher PSA, Gleason score, and rates of extracapsular extension and seminal vesicle invasion. After adjusting for these clinicopathologic variables in multivariate analysis, the luminal B subtype remained independently prognostic of unfavorable bRFS, DMFS, and PCSS.

The authors performed gene set enrichment analysis (GSEA) which demonstrated the androgen receptor (AR) pathway was enriched in luminal (A and B) tumors compared to basal tumors. They found that the luminal and basal subtypes had conserved markers for both luminal and basal lineages, respectively. Specifically, the basal CD49f signature was enriched in the basal cluster, while luminal markers NKX3.1, KRT18, and AR were enriched in the luminal subtypes.

Considering the observed variation in AR signaling, the authors hypothesized that luminal tumors may exhibit increased sensitivity to androgen deprivation therapy (ADT). They explored the predictive utility of PAM50 with respect to ADT response in patients who either did or did not receive androgen deprivation in the adjuvant/salvage setting. They performed an exploratory subgroup analysis by retrospectively matching clinicopathologic variables [Gleason score, PSA, lymph node involvement (LNI), extra-capsular extension (ECE), seminal vesicle invasion (SVI), and positive surgical margin status] and radiotherapy

treatment status in 315 patients treated with ADT (n=105) or not treated with ADT (n=210). For their analysis luminal A and basal subtypes were pooled and compared with the luminal B subtype.

Importantly the authors found that, with a median follow-up of 13 years, luminal B patients benefitted from postoperative ADT while luminal A and basal patients did not. In the luminal B subtype, which had the poorest prognosis, patients treated with ADT had improved DMFS (10-year metastasis rates: ADT, 33% *vs.* no ADT, 55%). On the other hand, non-luminal B subtypes treated with ADT had poorer DMFS compared with untreated patients (10-year metastasis rates: ADT, 37% *vs.* no ADT, 21%). Separating patients receiving adjuvant or salvage therapy in the matched cohort resulted in a similar trend, although no longer statistically significant, which the authors attributed to reduced numbers.

### The PAM50 classifier as a predictive biomarker

In addition to its established role in breast cancer, the PAM50 classifier has been successfully applied to bladder (17) and lung (18) cancer, where basal/luminal classification again appears to confer predictive value (19). Zhao and colleagues now show that PAM50 subtyping is able to stratify patient outcomes and may have value in predicting androgen response in prostate cancer (16). There are several notable limitations to the study reported by Zhao *et al.*, which the authors fastidiously point out in their manuscript. Most important among them is the retrospective nature of the study, rendering it impossible to completely account for confounders and selection bias.

In addition, a question arises as to why luminal B cancers would preferentially respond to ADT compared to luminal A tumors, which are similarly enriched for AR pathway activation. The authors maintain that luminal B tumors are biologically distinct from both basal and luminal A lineages with respect to proliferative index and expression of oncogenic drivers. Luminal B tumors represent a more aggressive subset, and therefore could be reasonably expected to exhibit a greater relative response to treatment intensification. However, the absence of any response to ADT in luminal A tumors remains incongruous with their AR activation state and represents an aspect in need of further study.

There are inherent limitations to taking a diagnostic optimized in one cancer and applying it to another. Breast and prostate cancer, while similar are not identical. A

priori, it is plausible that a more tailored *de novo* classifier embedded in the gene expression data may more accurately model risk and predict response in prostate cancer. Moreover, owing to methodological limitations, a measure of intra-tumoral heterogeneity is absent from this analysis. Basal and luminal subtypes are likely to co-exist within the same tumor, and may arise from a common progenitor, a phenomenon that has been described in organoid models of prostate epithelial differentiation and tumorigenesis (20).

Despite these limitations, the findings reported by Zhao and colleagues are promising and prospective validation of the utility of the PAM50 classifier in identifying the subgroup who might benefit from ADT is warranted. If confirmed, the PAM50 classifier may identify patients for the appropriate application of ADT in the post-operative setting. In the wake of recent randomized trials demonstrating a cumulative benefit to the addition of ADT in the post-operative recurrence setting (21,22), clinicians find themselves in need of tools to better identify exactly which men derive a benefit from concurrent ADT and salvage radiotherapy. Similarly, the optimal timing for initiation of ADT in pathologically node positive disease remains an open question (23). Given the parallels one can draw between breast and prostate cancer, it is not surprising that a uniform predictive algorithm may apply in both diseases. Based on its utility in breast, bladder and lung cancer, it stands to reason that the PAM50 gene expression classifier has more broad applicability and may transcend both tissue of origin, and perhaps even the basal/luminal framework, as a predictive tool in prostate cancer.

Prospective trials are needed to definitively establish the utility of the PAM50 classifier in prostate cancer. An upcoming cooperative group study, NRG-GU-006, will enroll patients with a rising PSA after prostatectomy, randomizing between salvage radiotherapy alone or salvage radiotherapy concurrent with a second-generation AR antagonist (apalutamide, ARN-509) (24). Importantly, this will be the first study in localized prostate cancer to stratify patients prospectively based on a predictive biomarker, the PAM50 classifier. This innovative study design should definitively answer the question of whether the PAM50 classifier can predict both prostate cancer outcomes and response to ADT in the post-operative setting.

### **Molecular profiling in prostate cancer: looking to the future**

As molecular stratification in prostate cancer comes of

age, and as cost barriers associated with clinical genomics become more permissive, emerging biomarkers may increasingly rely on more comprehensive integrative analyses. The Cancer Genome Atlas (TCGA) Research Network published their landmark report on the molecular taxonomy of primary prostate cancer in 2015 (25), wherein they examined genomic alterations, gene expression, and epigenetic changes in 333 primary prostate carcinomas. They found that 75% of primary prostate cancers fell into 1 of 7 subtypes defined by specific gene fusions (ERG, ETV1/4, and FLI1) or mutations (SPOP, FOXA1, and IDH1). These subtypes demonstrated substantial heterogeneity with respect to epigenetic profiles as well as AR activity, which clearly clustered in a subtype dependent manner. For example, the IDH1 mutant subset was associated with a hyper-methylator phenotype and SPOP and FOXA1 mutant tumors had the highest levels of AR-induced transcripts. In addition, 25% of the prostate cancers they examined had “actionable” lesions in the PI3K or MAPK signaling pathways. They also found DNA repair genes inactivated in 19% of localized prostate cancers. This degree of molecular heterogeneity infers the existence of distinct taxonomies, defined by genomic alterations, transcriptional states, and epigenetic marks, conferring differential sensitivity to therapies such as ADT, chemotherapy, and radiation therapy.

Integrative molecular biomarkers will play an increasingly important role in risk stratification for clinical decision making in prostate cancer. Scenarios posing management dilemmas in contemporary multidisciplinary prostate cancer clinics include: (I) which men with favorable risk disease can be safely observed; (II) which men with unfavorable risk localized disease need treatment intensification, for example with a combination of surgery, radiation and androgen deprivation; (III) which men receiving salvage therapy will benefit from concurrent androgen deprivation and for how long; (IV) which men with low volume metastatic disease may be rendered disease free with combinations of systemic therapy and local therapy; and (V) how to best sequence available systemic therapies in men with castrate resistant metastatic prostate cancer. These scenarios are becoming both increasingly common and more complex as clinicians attempt to incorporate novel functional imaging modalities and new therapies, including DNA damage response modulators and immunotherapy.

In conclusion, the incorporation of molecular profiling in the management of prostate cancer is entering the mainstream. As such, a working knowledge of emerging

molecular diagnostics is fast becoming a pre-requisite for contemporary high-quality care of the prostate cancer patient.

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