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Review article

Genomic, pathological, and clinical heterogeneity as drivers of personalized medicine in prostate cancer

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Abstract

Prostate cancer (CaP) is the most commonly diagnosed malignancy in men in the Western world. In North America, more than 275,000 men are diagnosed annually, whereby approximately 1 in 6 men will be diagnosed with CaP in their lifetime, and 1 in 34 men will die from castration-resistant metastatic disease. Unfortunately, current clinical prognostic factors explain only a proportion of the observed variation in clinical outcome from patient to patient. Furthermore, overtreatment of indolent and low-risk cancers leads to inappropriate morbidity following radiotherapy or surgery. As such, better predictors of individualized prognosis and treatment response are urgently needed to triage patients to customized and intensified CaP treatment. Recent developments in next-generation sequencing have made it possible to identify prognostic and predictive signatures based on genomic profiles. We discuss the genetic basis of CaP progression from localized to systemic disease (e.g., point mutations, copy-number alterations, and structural variants) in relation with unique features of CaP biology, including intraprostatic and interprostatic heterogeneity, multifocality and multiclonality, TMPRSS2:ERG, and other ETS-family gene fusions. Finally, we focus on the use of genomic markers as prognostic factors for local failure and for systemic disease, as novel risk-stratification tools, in triaging patients to existing treatment options, and ultimately the potential of genomics for the identification of molecular targets for therapy of CaP.

Keywords: Prostate cancer; Genomics; Prognosis; Radiotherapy; Surgery; Personalized cancer medicine; Molecular oncology; Heterogeneity

1. The need for genomics in prostate cancer prognosis

Prostate cancer (CaP) is the most commonly diagnosed malignancy in men in the Western world, with 1 in 6 men diagnosed with CaP and 1 in 34 dying of metastatic disease. In North America and Europe, over 500,000 cases are diagnosed annually [1,2].

Treatment options for CaP depend on the TNM staging of the disease. Using the prognostic variables of T category, serum prostate-specific antigen (PSA), and Gleason score (GS), men with localized CaP are placed in low-, intermediate-, and high-risk groups. These risk groups predict for biochemical relapse (also referred to as biochemical relapse-free rate based on posttreatment increases in PSA level) and prostate cancer–specific survival [3].

In localized CaP of low or intermediate risk (Fig. 1), treatments such as active surveillance, radical prostatectomy, and radiotherapy (RT) (either external-beam RT or brachytherapy) are used. The choice of treatment would depend on patient preference and other considerations (e.g., operative risk and co-morbidities). In some patients initially managed with radical prostatectomy (e.g., with positive

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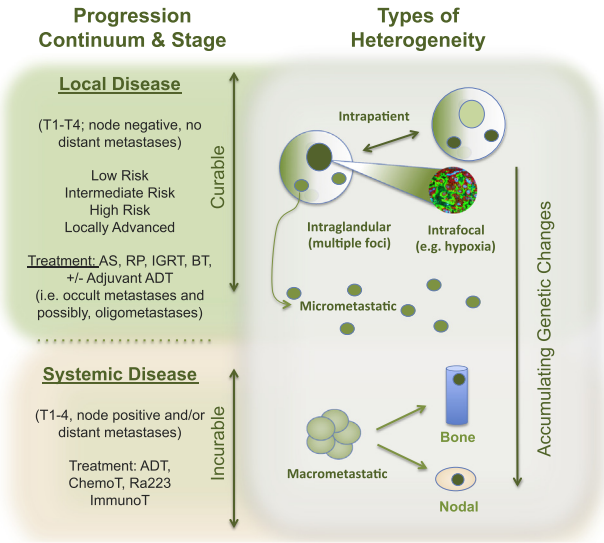

Fig. 1. Sources of heterogeneity in prostate cancer. Interpatient heterogeneity exists throughout the progression from localized, potentially curable disease to incurable, castration-resistant disease and may be related to both interfocal and intrafocal factors.

surgical margins, extracapsular extension or persistent or rising PSA level or both during follow-up), adjuvant or salvage RT to the prostatic fossa has proven effective [4,5]. Patients with high-risk disease are commonly managed with surgery or RT in combination with androgen deprivation therapy owing to the increased risk of subclinical distant metastases. Finally, for men who develop metastatic or recurrent disease, palliative noncurative treatment has led to improved progression-free survival and includes continuous androgen deprivation, chemotherapy using docetaxel and prednisone, secondary hormonal manipulation using enzalutamide or abiraterone, systemic radionuclides (Ra223), and immunotherapy (sipulcel-T). Further improvement in pain symptomology can be achieved with targeted, palliative RT (8-Gy single dose or 20–30 Gy in daily fractions) [1,6]. At present, there are few, if any, predictive biomarkers to differentiate the use of a systemic agent vs. another, either as a single or as a combined treatment [7].

2. Heterogeneity of clinical outcomes

The current clinical prognostic factors of T category, PSA, and GS explain only a moderate proportion of the observed heterogeneity in clinical outcome [2]. The use of PSA alone to determine the clinical course in otherwise "clinically silent" disease needs to be buttressed with biomarkers based on tumor biology [1]. For example, biochemical relapse can range from 20% to 60% in intermediate- and high-risk patients treated with precision RT or surgery alone [8,9]. There are no tests currently used in the clinic that can differentiate patients who will be cured by local therapy alone vs. patients who need combined modality treatments as a means of intensification therapy due to predicted local or systemic resistance or both. Further complicating the issue for personalized medicine is the fact that many low-risk CaP cases are indolent and their overtreatment can result in significant morbidity. For example, up to two-thirds of low-risk CaP cases can be followed without treatment when reliably triaged to active surveillance alone, thereby preventing severe treatment-related complications and gastrointestinal, genitourinary, and sexual function side effects of RT or surgery. However, it appears that within 7 to 10 years one-third of these low-risk patients are being reclassified as intermediate risk mainly as a consequence of sampling bias causing undergrading of their cancer in the initial prostate biopsy, whereas subsequent biopsies show a higher grade or more extensive CaP [10]. Multifocality and tumor heterogeneity of CaP underlie this unresolved issue of prostate biopsy sampling bias at the time of diagnosis. Here again, on an individualized basis, there are few validated tests that predict a priori which patients have indolent vs. aggressive localized disease that would lead to deintensification and intensification treatment strategies. Therefore, better predictors of treatment outcome and patient prognosis are required to individualize CaP treatment and to provide the optimal therapy with minimal side effects.

3. Defining heterogeneity in CaP: Multifocality and multiclonality

CaP is unique in that it is a multifocal cancer with clonal subpopulations and varied histological and molecular abnormalities that can determine whether cancers are relatively indolent or aggressively metastatic. Heterogeneity exists both within and between patients (Fig. 1); indeed, $\sim$80% of prostatectomy specimens contain >1 disease focus [11,12]. It is, therefore, critical to define genetic heterogeneity that exists within a given prostate gland—and within a given focus of cancer—as pathological staging criteria do not adequately account for heterogeneity of this type.

"Aggressive" CaP can be defined as those cancers that harbor biology associated with local resistance to RT or an early distant metastatic spread capacity or both that increases patient lethality and decreases prostate cancer–specific survival. Recent studies have identified specific lesions found in primary vs. metastatic disease [13], and although the number of patient-matched primary/metastatic tumors analyzed to date is small, these studies have the potential to shed light on the origins of metastasis in CaP. For example, several studies have shown that anatomically distinct tumor metastases are derived from a single progenitor clone (Table 1) [14–16]. Distant bone metastasis is the most common pattern of CaP spread, but a subset of CaPs has the ability to spread to soft tissue. It remains unclear whether differential metastasis to bone vs. soft tissue can be predicted a priori based on the genetic signature of a tumor.