**Precision, complexity and stigma in advanced prostate cancer terminology: it is time to move away from "castration resistant" prostate cancer.**

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IDD is supported by an NHMRC Practitioner Fellowship (APP1102604).The treatment of men with advanced prostate cancer (APC) is changing rapidly, with several new therapeutic options leading to longer survival. Categorizing clinical states that reflect the cancer biology and prior therapy in men with APC has become more complex. The Prostate Cancer Clinical Trials Working Group (PCWG2) developed guidelines that harmonized inclusion, monitoring and outcome definitions for clinical trials in APC [1-3]. PCWG2 guidelines were seminal in changing the terminology from ‘hormone-refractory’ or ‘androgen-independent’ to ‘castration-resistant prostate cancer (CRPC)’, based on evidence of men responding to further hormonal manipulations after primary androgen deprivation therapy (ADT). Both of the approved next-generation endocrine agents, abiraterone acetate and enzalutamide, have shown an overall survival benefit for men with progressive cancer despite castrate levels of testosterone [4, 5]. Thus, adopting the term ‘castration-resistant’ improved the biological accuracy of disease characterization compared to ‘hormone refractory’. The term CRPC, although not unanimously accepted, has become embedded in research and clinical practice.

However, the expression “castration” has strong negative connotations, even if biologically appropriate [6]. The term is used more commonly in veterinary medicine, and it has punitive associations among a variety of cultures, where castration has been used in the past as a means of inducing punishment and/or submission. Many clinicians have experienced negative responses from men and their families when using the term castration-resistant prostate cancer. As the clinical and research communities strive to maximize patient-centered care and involve men in treatment decision making [7], it is time to acknowledge that the label we have assigned to their disease state may be alienating to the very men we are trying to engage.

Upfront use of docetaxel with ADT as chemo-hormonal therapy has become a standard of care for men with newly diagnosed metastatic prostate cancer [8-11]. Recently, abiraterone has been proven to provide similar survival benefits when administered from commencement of ADT [12, 13]. Additionally, there are a number of ongoing clinical trials investigating earlier use of enzalutamide and other AR-targeted therapies or combinations prior to the onset of “castration resistance”. According to PCWG3 criteria, a patient treated upfront with ADT/docetaxel or ADT/abiraterone would theoretically be in the same first-line metastatic CRPC category upon progression as a man treated with ADT alone, but it is unlikely that the resistant tumors that eventually emerge are biologically similar. Resistance mechanisms to AR targeting agents have been described in the castration resistant setting and it seems likely that similar and perhaps additional mechanisms of resistance may occur when these agents are used earlier [14, 15].

It is evident that the term CRPC currently encompasses diverse populations; this diversity will only increase as the therapeutic approach evolves and an expanding range of treatment combinations and sequences become available. The time is ripe to update the terminology. The ideal terminology may best be identified by engaging not only clinicians, but by also involving consumer and advocacy groups to identify terms that will simultaneously satisfy men with APC, as well as reflecting the biology and prior treatment of the disease.

One possible option for the prostate cancer community would be to begin by referring to metastatic or advanced prostate cancer, specify each line of treatment and molecular subtype, analogous to terminology used in defining subtypes and treatment lines in breast cancer [16]. The description would therefore include “metastatic prostate cancer” followed by treatments received/receiving. Additionally if appropriate this can be complemented by a defined molecular state e.g. “with germline BRCA2 truncating mutation”. This will also allow greater flexibility if gonadal suppression is one day replaced by novel treatments that do not act by suppressing testosterone levels, such as advanced single agent androgen receptor blockade [17]. Most importantly, the term would not reflect upon the gonadal status of the individual, but would serve to describe the disease without implications about the virility of the individual.

“CRPC” was terminology that was aligned with our interventions and registration strategies, when our therapeutic approach to non-localized prostate cancer was linear. However, the rapid development of new agents and approaches that are no longer used in a fixed order, and which undoubtedly will be used in an increasingly complex non-linear fashion, make the term less relevant. This process reflects a movement towards precision oncology, where the imperative is no longer to group men in large homogenous groups, but rather, to acknowledge the diversity of biology and therapies available.

Thus, we advocate discontinuing the use of the term “CRPC” and replacing it with more descriptive nomenclature, in an effort to simultaneously increase the precision in our terminology, acknowledge the complexity of advanced prostate cancer, and move away from stigmatizing language. Importantly we propose partnering with patients and advocates to develop appropriate terminology that is not viewed negatively by the men who entrust us with their care. It is time to make this change.

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