Evolving understanding and categorization of prostate cancer: preventing progression to metastatic castration-resistant prostate cancer: RADAR IV

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Introduction: To interpret data and update the traditional categorization of prostate cancer in order to help treating clinicians make more informed decisions. These updates include guidance regarding how to best use next generation imaging (NGI) with the caveat that the new imaging technologies are still a work in progress.

Materials and methods: Literature review.

Results: Critical goals in prostate cancer management include preventing or delaying emergence of distant metastases and progression to castration-resistant disease. Pathways for progression to metastatic castration-resistant prostate cancer (mCRPC) involve transitional states: nonmetastatic castration-resistant prostate cancer (nmCRPC), metastatic hormone-sensitive prostate cancer (mHSPC), and oligometastatic disease. Determination of clinical state depends in part on available imaging modalities. Currently, fluciclovine and gallium-68 (68Ga) prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) are the NGI approaches with the most favorable combination of availability, specificity, and sensitivity. PET imaging can be used to help guide treatment selection in most patients. NGI can help determine patients who are candidates for new treatments, most notably (next-generation androgen antagonists, eg, apalutamide, enzalutamide, darolutamide), that can delay progression to advanced disease.

Conclusions: It is important to achieve a consensus on new and more easily understood terminology to clearly and effectively describe prostate cancer and its progression to health care professionals and patients. It is also important that description of disease states make clear the need to initiate appropriate treatment. This may be particularly important for disease in transition to mCRPC.

Key Words: androgen antagonist, biomarker, imaging, metastasis, sequencing

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Introduction

The traditional categorization of prostate cancer is limited by outdated scanning technology, a lack of
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standardized molecular and biologic markers of disease progression, and uncertainty regarding the impact of genetic alterations both prognostically and in response to therapy. However, new information is emerging that can help clarify the way we characterize the disease.

The Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group was originally convened to help provide a bridge between current prostate cancer guidelines and practical clinical decision making. The goal of this paper is to continue that tradition by interpreting new data and updating the traditional categorization of prostate cancer in order to help treating clinicians make more informed decisions. These updates include guidance regarding how to best use the next generation imaging (NGI) with the caveat that the new imaging technologies are still a work in progress.

Materials and methods

The RADAR IV Group convened to evaluate the use of NGI modalities for assessment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) and nonmetastatic castration-resistant prostate cancer (nmCRPC) and to review results from studies evaluating newer agents, primarily next-generation androgen receptor inhibitors, for delaying progression to metastatic castration-resistant prostate cancer (mCRPC). Recommendations were also made regarding prostate cancer nomenclature to accurately represent transitional disease states and guide treatment decision making.

Results and discussion

Critical goals in prostate cancer management include prevention of distant metastases and progression to castration-resistant disease. Pathways for progression to mCRPC involve nmCRPC and mHSPC. Data from the placebo arms of randomized clinical trials indicated that 33% to 46% of men with nmCRPC developed ≥ 1 bone metastasis after 2 years.1,2 The risk for this event increases dramatically in patients with nmCRPC with prostate-specific antigen doubling time (PSADT) < 8 months.3 In patients with mHSPC receiving androgen deprivation therapy (ADT) alone, progression to mCRPC occurs in approximately 11.7 to 15 months.4

The transitions from nmCRPC or mHSPC to mCRPC are seminal events in disease and are associated with significantly decreased survival. A retrospective analysis of 450 men with biochemically recurrent prostate cancer following prostatectomy indicated that 140 developed subsequent metastases. Metastasis-free survival (MFS) was 10.2 years and median overall survival (OS) after metastasis was 6.6 years. Longer MFS (HR = 0.77; 95% CI 0.63-0.94) and lower metastatic burden (≤ 3 versus ≥ 4 metastases; HR = 0.50; 95% CI 0.29-0.85) were independent predictors of OS.5 The International Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group combined results from 28 clinical trials to demonstrate that the emergence of metastases in patients with localized prostate cancer was associated with decreased OS.6 Results from 28,905 followed for a median of 10 years showed that 45% of 12,712 men experienced a MFS and OS was 0.91. Results from a retrospective longitudinal cohort study of 1236 patients with nmCRPC also indicated a significant relationship between MFS and OS (r = 0.62, p < 0.0001).7

In patients with mHSPC, a shorter time to castration resistance is significantly associated with shorter OS.8 A study of 437 consecutive patients with mHSPC whose primary ADT had failed divided them into four groups with times to castrate resistance of 0-6, 6.1-12, 12.1-18, and ≥ 18.1 months, respectively. The OS from diagnosis was 40.8, 57.1, 62.2, and 70.1 months, respectively, in the four groups (p < 0.001).8 Progression to mCRPC is also associated with decreased quality of life9-11 and increased cost of care.12 An important question that needs to be addressed is whether there is a role for NGI as part of consolidative strategies earlier in the disease and which of them may offer long term benefit.

Evolution of patient assessment and risk stratification for progression to mCRPC

In the clinical states model for prostate cancer that is often depicted, Figure 1,13 disease is characterized as a dynamic continuum and it is often unclear when transitions from one clinical state to another occur. Earlier recognition of disease transitions is needed to document earlier relapse and to provide a rationale for the study of consolidative approaches that may lead to durable responses.

Localized HSPC and biochemically relapsed disease
Each prostate cancer has an inherent biology such that no two cases behave similarly, even when matched for Gleason group, prostate-specific antigen (PSA), and patient age. NGI has been used in an effort to detect recurrent disease in situations where the biological likelihood of recurrence is low (eg, slowing rising PSA of 0.1-0.5 ng/dL postprostatectomy). Both fluciclovine and prostate-specific membrane antigen (PSMA) positron emission tomography (PET) offer the potential
Figure 1. Traditional approach to categorization and description of prostate cancer.\textsuperscript{13}

to detect disease within and outside the prostate bed (e.g., within the anastomosis or the pelvic lymph nodes). Disease in these disparate locations has differing treatment implications. Anastomotic disease may require radiation limited to the prostate bed, while nodal disease detected outside the bed may prompt radiation to both the bed and pelvic basin, and addition of ADT. However, PSMA PET imaging does not detect all foci of disease, thereby leading to confusion about how to best treat two potentially biologically disparate cancers.

\textit{De novo} mHSPC is characterized by shorter time to development of castration resistance and worse OS versus primary progressive prostate cancer.\textsuperscript{14,15} Patients with mHSPC have heterogeneous biological and clinical patterns, ranging from indolent disease (asymptomatic patients with low tumor burden) to more aggressive cancer (high Gleason score, low PSA values, symptomatic patients with extensive bone involvement and/or visceral metastases).\textsuperscript{16} At present, there is no validated prognostic classification that encompasses clinical and histopathological features with the aim of predicting clinical outcomes for mHSPC.\textsuperscript{16} The recently published American Society of Clinical Oncology (ASCO) guidelines for NGI state these modalities might aid in clarifying the burden of disease and support choosing between multimodal management of oligometastatic disease and systemic anticancer therapy alone or in combination with targeted therapy for palliative purposes.\textsuperscript{17}

The oligometastatic state

Definitions of oligometastatic disease at diagnosis remain controversial and can range from 4-5 to as many as 10 metastatic bone lesions. Oligometastatic disease at diagnosis can be defined by the extent of nodal station involvement. While some surgeons perform lymphadenectomies extending up to the iliac nodes during prostatectomies, others may defer them to a later time or in the setting of biochemically relapsed disease.

\textit{nmCRPC}

Definition of high risk in nmCRPC has focused on PSA levels and their rate of increase. A study of 201 patients with nmCRPC showed that baseline PSA level > 10 ng/mL and PSA velocity were both correlated with time to detection of first bone metastasis\textsuperscript{1} and all three of the studies of next-generation antiandrogens used a PSADT ≤ 10 months (~70% had a PSADT < 6 months) while receiving ADT and no distant metastases on conventional imaging as inclusion criteria.\textsuperscript{18-20} About 30\% of patients with nmCRPC would be classified as being at high risk for the development of metastases on the basis of PSADT.\textsuperscript{21,22}

Treating where no one has gone before: new developments in the use of NGI

Determination of clinical state, particularly distinguishing between nmCRPC and mCRPC, depends in part on available imaging modalities. CT and bone scan (BS) have limited ability to detect prostate cancer dissemination to lymph nodes and bone\textsuperscript{23-25} and more sensitive molecular and functional imaging can help define the true extent of disease, detect small foci of relapse, and decrease the size of the “true” nmCRPC population.\textsuperscript{25-27} In one recent
Molecular and genomic biomarkers

Molecular and genomic biomarkers have potential for application in all prostate cancer stages. A review of biomarkers with potential importance in mHSPC indicated that those indicative of aggressive or metastatic disease (alterations in PTEN, TP53, FOXA1, PIK3CA, APC, and BRCA2) did not differ significantly between de novo mHSPC and mCRPC, but it has been shown that wild type for PTEN/RB1, p53, or HSD3B1 is associated with a more favorable prognosis in mHSPC. Assessment of tumors from patients enrolled in STAMPEDE indicated that PTEN deficiency was observed in 34% of patients (25% copy number loss, 9% mutation). TP53 mutation or loss occurred in 33%, aberrations in phosphoinositide 3-kinase (PI3K) signaling in 16%, mutated genes involved in DNA repair in 14%, altered Wnt signaling in 14%, and dysregulated cell cycle control in 6%. Overall, genetic aberrations were observed in 76% of patients, with 35% harboring two or more mutations.

There is little information about clinically relevant molecular biomarkers in nmCRPC. Results from transcriptome-wide profiling of primary tumor samples from patients in the SPARTAN trial using the DECIPHER prostate test and assessment of associations between scores and subtypes from previously derived prognostic and predictive gene signatures (eg, DECIPHER and basal (BA) versus luminal (LU) subtyping) indicated that patients with higher DECIPHER scores had greater treatment effects with apalutamide plus ADT than those with low scores. Patients with either LU or BA subtypes benefited from apalutamide plus ADT.

Biomarker evaluation is also important in mCRPC. It has been suggested that patients positive for homologous recombination DNA damage repair (DDR) gene mutations (BRCA1, BRCA2, ATM, PALB2, and CHEK2) should be considered for enrollment in a clinical trial or treated with a poly (ADP-ribose) polymerase (PARP) inhibitor or platinum-based chemotherapy. Results from the PROfound trial support the use of a PARP inhibitor, olaparib, in patients with mCRPC and specific DDR mutations. In patients with mCRPC and homologous recombination...
repair alterations \textit{BRCA1}, \textit{BRCA2}, or \textit{ATM}, olaparib improved radiographic progression-free survival (rPFS) and objective response rate compared to enzalutamide/abiraterone, with a favorable trend for OS despite crossover. It should be noted that the results for \textit{ATM} have yet to be replicated.\textsuperscript{25,42} Biomarkers related to immunologic interventions have also received attention in mCRPC. Programmed death ligand 1 expression and \textit{CDK12} and microsatellite instability-high are highly prevalent in high-risk prostate cancer\textsuperscript{43} and results from KEYNOTE 199 showed that pembrolizumab has antitumor activity and provides disease control in bone-predominant mCRPC previously treated with docetaxel.\textsuperscript{44}

Epigenetic markers have also been shown to have prognostic value in prostate cancer. Analysis of hypermethylation patterns of 2 genes (\textit{GSTP1} and \textit{APC}) in plasma cfDNA of patients with CRPC and their kinetics after starting treatment showed that patients with baseline marker levels below median had significant fewer prostate cancer-related deaths (p < 0.02) and did not reach the median survival point.\textsuperscript{45}

Preventing progression to mCRPC

Results from multiple studies, particularly those assessing next-generation antiandrogens, have demonstrated that it is possible to significantly delay progression to mCRPC and change the standard of care for patients with either mHSPC or nmCRPC.

\textit{nmCRPC}

Until recently, patients with nmCRPC and rising PSA despite a low testosterone level on ADT were managed either with endocrine manipulations (without a proven survival benefit) or watched with repeated PSA testing. The European Association of Urology (EAU) guidelines did not recommend treatment for such patients outside a clinical trial setting.\textsuperscript{46} These approaches are no longer acceptable for men at high-risk of developing mCRPC.\textsuperscript{46} Addition of next-generation antiandrogens (eg, apalutamide, enzalutamide, darolutamide) to ADT in men with nmCRPC based on conventional imaging significantly delays progression to mCRPC. The SPARTAN trial that included 1207 men with nmCRPC and a PSADT < 10 months (NCT01946204) indicated that the median MFS was 40.5 months with addition of apalutamide to ADT versus 16.2 months for placebo added to ADT (HR for metastasis or death = 0.28, 95% CI 0.2-0.35, p < 0.001). At 41 months of follow up, apalutamide plus ADT was associated with improved OS versus placebo plus ADT (HR = 0.75, 95% CI 0.59-0.96, p = 0.0197).

We now have new tools to identify metastatic disease
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Figure 2a. Prostate cancer clinical states model, updated for the PCWG3. This model considers mCRPC in terms of number of lines of prior therapy rather than in relation to docetaxel treatment and emphasizes the importance of serial biologic profiling of the disease at the start of a new therapy and time of progression.59,60 Reproduced with permission. © 2016 American Society of Clinical Oncology. All rights reserved.

Figure 2b. Clinical disease states of prostate cancer.61 Source: Hala Borno, MD, BS. Modified with permission.

and assist in establishing a prognosis for patients with mHSPC or nmCRPC26,49,50 and novel therapeutic regimens that are effective for delaying progression to mCRPC.51 These advances prompt reconsideration of how we categorize and describe prostate cancer.

Traditional categorization of prostate cancer is most often focused on five factors: Gleason score and more recently Grade grouping, tumor burden, PSA level, emergence of resistance to specific treatments (eg, ADT), and the presence or absence of metastases, Figure 1.52-54 This prostate cancer categorization and description of progression is insufficient for classification of disease and guiding selection of treatment.55-57

It has been suggested that a “model” of prostate cancer should fill four distinct needs.58 It should: 1) describe the progression of prostate cancer from diagnosis to death; 2) include a representation of both the natural and treated history of the disease and provide a framework for iterative reassessment of prognosis over time; 3) have a small number of clearly defined and mutually exclusive disease states; and 4) support clinical decision making based on the risk of disease progression. An additional issue that should be addressed in describing prostate cancer is how increased understanding of disease progression emerging from NGI should be incorporated; that is, how should we go forward with an “imaging state.”

Recognition of the need for a simple staging system to guide care has prompted several initiatives aimed at achieving this goal. The PCWG3 (prostate cancer working group 3) consensus proposed a clinical states model, Figure 2a59,60 that distinguishes between prostate adeno- and nonadenocarcinomas; considers the sequence and number of prior systemic therapies rather than only pre- and post-taxane distinctions; encourages reporting of disease subtypes; and defines endpoints for patients transitioning between nonmetastatic and metastatic disease. It also emphasizes consideration of patient-reported outcomes, rPFS, assessment of circulating tumor cells, and time to clinical events rather than alterations in individual biomarkers. It underscores the distinction between first evidence of progression based on one disease manifestation versus stopping therapy because the patient no longer appears to be receiving benefit.59,60 A similar and even simpler scheme has been put forward by Cancer Care Ontario, Figure 2b.61

Paller and Antonarakis developed a proportional prostate cancer clinical states model adapted from the prostate cancer clinical states model59 and the
Oncologic drivers of progression promote tumor heterogeneity and tumor immune resistance. Targeting driver pathways may enhance the effectiveness of immunotherapies.65,66 This image is used under a Creative Commons CC BY 4.0 License.

Additional schemes have overlaid information regarding specific oncologic driver pathways and potential targets for intervention with immunologic agents, Figure 2d.64,65 Additions of this type are likely to play a greater role in treatment as targeted and immunologic treatments are evaluated and validated in clinical trials.

We suggest combining information from the approaches of Paller63 and PCWG360 and dividing prostate cancer into four states: localized disease, biochemically recurrent disease, transitional disease, and advanced disease, Figure 3. The term “transitional” transitional states. Definition of a transitional disease state is meaningful, not only because of differences in biology and prognosis versus advanced prostate cancer, but also because newly approved therapies can significantly extend the duration of transitional disease and delay the adverse consequences of progression to advanced disease. These transitional states are dynamic and transitions may occur rapidly. This mandates the use of the most sensitive imaging techniques to capture and characterize them and gain prognostic and predictive information to guide treatment.

Oligometastatic prostate cancer (presence of ≤ 5 metastatic sites) might also be considered as a transitional

Figure 2c. Proportional prostate cancer clinical states model. The circles represent the proportional prevalence of each disease state.63 Reproduced with permission.

Figure 2d. Oncologic drivers and targets for immunotherapy along the course of prostate cancer progression. Oncogenic drivers of progression promote tumor heterogeneity and tumor immune resistance. Targeting driver pathways may enhance the effectiveness of immunotherapies.65,66 This image is used under a Creative Commons CC BY 4.0 License.
state, but this is open to debate. It has been suggested that oligometastatic prostate cancer may represent cancer that is slow growing and/or has limited metastatic potential or simply early detection of metastases due to more sensitive imaging modalities.\textsuperscript{71} There is no clear consensus on oligometastatic disease as a discrete entity, its prevalence, or how it should be treated. In addition, there is no consensus on the role of imaging to define or manage oligometastatic disease. It has been suggested that some patients with a limited number of metastases might be cured if all of them are eradicated,\textsuperscript{72} but evidence supporting use of focal therapies in management of oligometastasis is limited.\textsuperscript{72–74}

Sequencing therapy

ASCO has recommended that NGI can be offered to men with nmCRPC only if a change in the clinical care is contemplated.\textsuperscript{17} NGI may clarify the presence or absence of metastatic disease in these patients and provide guidance in treatment selection and sequencing.\textsuperscript{27} Results summarized in this paper support the utility of apalutamide along with darolutamide and enzalutamide in nmCRPC; and treatment with apalutamide and enzalutamide in patients with mHSPC. In addition, olaparib should be considered as first-line treatment in patients with mCRPC with DNA-repair abnormalities (advanced disease) once it is approved by regulatory authorities. In sequencing therapy, it is important to consider how use of a given agent in one line may influence the choices that remain available for subsequent lines. Use of next-generation antiandrogens can result in a phenotypic shift in advanced prostate cancer (mCRPC) characterized by the emergence of an androgen receptor (AR)-null neuroendocrine-null phenotype. These “double-negative” prostate cancer’s have elevated fibroblast growth factor (FGF) and mitogen-activated protein kinase (MAPK) pathway activity, which can bypass AR dependence. Pharmacological inhibitors of MAPK or the FGF receptor repress the growth of double-negative prostate cancer’s \textit{in vitro} and \textit{in vivo} and FGF/MAPK blockade may be efficacious against metastatic prostate cancer’s with an AR-null phenotype.\textsuperscript{66} Results from the CARD trial have also shown that attempting to sequence antiandrogens (enzalutamide after abiraterone or vice versa) in advanced prostate cancer treated with one of these agents plus docetaxel is significantly less effective than switching to cabazitaxel with respect to both OS and PFS.\textsuperscript{75}

Treatment selection and sequencing should also consider safety and tolerability. Emergence of
hypertension occurs frequently with next-generation antiandrogen agents and patients should be monitored for this complication.76,77 There is less information about the safety of PD-1 inhibitors in patients with prostate cancer. KEYNOTE-028 included 23 patients treated with pembrolizumab and 3 had a total of 4 grade 3/4 adverse events that included asthenia, lipase elevation, peripheral neuropathy, and fatigue.78 Sipuleucel-T is generally well tolerated. Events that have been reported to the FDA include chills, malaise, pyrexia, fatigue, and nausea. Infusion-related reactions, infections, vascular events, and transient ischemic attacks were reported at higher than expected levels.79 Adverse events reported in patients treated with Ra-223 include diarrhea (25%), nausea (36%), anemia (31%), and thrombocytopenia (12%, grade 3-5 in 7%).80

Maintenance of bone health is a critical issue in the treatment of men with prostate cancer and it has received significant attention due to the adverse effects of ADT.81 It should be monitored closely in patients receiving the newer agents considered here. Addition of bone-protecting agents to radium-223 treatment can limit fractures in men with mCRPC, especially those treated concomitantly with advanced hormonal agents, such as abiraterone acetate plus prednisone.82

Conclusions

Delaying progression to advanced disease is an important and achievable goal for patients with transitional prostate cancer and NGI can permit earlier identification of these patients and refine risk stratification. It is important to achieve a consensus on new and more easily understood terminology to communicate with health care professionals and patients to clearly and effectively describe prostate cancer and its progression. It is also important that description of disease states make clear the need to initiate appropriate treatment. This may be particularly important for transitional disease.

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