

The Evolving Landscape of Prostate Cancer Management

BRCA Testing and ctDNA as Diagnostic Tools and PSMA-Imaging and -Targeted Approaches



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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Analyze the evolution of prostate cancer management from acute to chronic, identifying key challenges in treating advanced stages.
- Evaluate the role of emerging biomarkers and targets, especially PSMA, in improving detection and treatment of metastatic castration-resistant prostate cancer.
- Assess how precision medicine has transformed prostate cancer care across the disease spectrum, from risk assessment to advanced disease management.

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Prostate cancer remains the most common tumor type in males and the second leading cause of cancer deaths overall in the United States.¹ With an estimated 299,010 new cases expected in 2024, the average lifetime risk of diagnosis is about 17%, while the risk of dying from the disease is approximately 3%.

The landscape of prostate cancer management has been dramatically reshaped by precision medicine. This approach has evolved from focusing on individual risk assessment to guiding diagnostic procedures, treatment decisions, and management of advanced disease.²

Precision medicine now incorporates:

- **Risk assessment:** Utilizing genetic and molecular markers to identify high-risk populations
- **Diagnostic accuracy:** Employing advanced imaging techniques and biomarker analysis to enhance prostate biopsy procedures
- **Tailored treatments:** Optimizing therapy based on the genetic profile of the tumor, balancing efficacy with minimized adverse effects
- **Advanced care strategies:** Personalizing treatment for advanced prostate cancer using targeted therapies, immunotherapies, and hormone-based treatments aligned with the molecular characteristics of the tumor

Q / Which patient subpopulation would you test for BRCA1/2 mutations?

HUSSAIN / Anytime we have patients who have metastatic disease, testing them for *BRCA* or *BRCA*-like genes is going to be important, potentially for therapeutic purposes and particularly in metastatic castration-resistant disease. Other than that, testing for germline mutations is important.

Q / How do you foresee the role of circulating tumor DNA (ctDNA) as a diagnostic and prognostic tool in prostate cancer?

HUSSAIN / Potentially, ctDNA will play different roles. In situations in which we are looking for insight into the genomics of the tumor, ctDNA is going to be helpful in that regard. When it comes to the actual diagnosis of prostate cancer or the staging of disease, ctDNA is not a mature biomarker at this point. For diagnostic purposes, we need the tissue either via biopsy from the prostate or, if a patient has metastatic disease, then biopsy from tissues affected by metastasis. As it relates to monitoring disease activity, prostate-specific antigen (PSA) continues to be the most useful biomarker.

Any additional biomarkers, such as ctDNA, will have to be validated as they relate to early detection of metastatic disease or micrometastatic disease and potential response to therapy.

Q / How have PSMA diagnostics changed the way that prostate cancer is managed?

Despite these advancements, detecting recurrence and treating metastatic disease remain significant challenges.³ Conventional imaging often falls short in early detection, and hormone-resistant tumors present a major clinical obstacle. However, new hope lies in targeting prostate-specific membrane antigen (PSMA), which is frequently overexpressed in prostate cancer.⁴ PSMA-targeting molecules are being developed to both detect early metastasis and treat metastatic castration-resistant prostate cancer (mCRPC), potentially offering new avenues for managing this challenging stage of the disease.⁵

As research continues, the integration of these precision medicine approaches and novel targeted therapies promises to further improve patient outcomes and quality of life for those affected by prostate cancer.

HUSSAIN / From a therapeutic standpoint, it provides an option that we did not have for patients before. Since 2004, when the first drug that prolonged life in castration-resistant disease—docetaxel—was approved, we now have infinitely more agents available for our patients. I'm hopeful that at some point we're going to have potential cures for patients with metastatic disease.

Use of PSMA therapeutics, specifically, is an FDA-approved option based on impactful benefit with regard to progression-free survival and overall survival in the setting of end-stage mCRPC.

The imaging is very important. Ultimately, the goal is to detect cancer at a very early stage with the hope that we can target it, treat it appropriately, and potentially cure it. I do think that theranostics with regard to the imaging component is very helpful. However, it is clear that more research to define its impact on our treatment decisions is needed. Until now, when it comes to metastatic disease, all of the current data from key clinical trials that led to FDA approvals and guiding our therapy decisions were based on conventional imaging and not PSMA imaging.

I tell patients and my mentees: in reality, a tumor 1 cm³ in size is comprised of a billion cancer cells. Clearly, even if the PSMA

TABLE. Emerging Agents of Next-Generation Imaging in Prostate Cancer⁴

RADIOTRACER	ADVANTAGES	DISADVANTAGES	STATUS
⁶⁸Ga-PSMA-11	<ul style="list-style-type: none"> • Lower uptake time. • Lower radiation exposure. • Extensively researched. • TLX591-CDx radiopharmaceutical cold kits will enable greater accessibility. 	<ul style="list-style-type: none"> • ⁶⁸Ga generator–dependent production makes mass production relevant to ¹⁸F–based agents. • Difficult to transport due to short half-life. 	Received FDA approval (currently only covers UCSF and UCLA).
⁶⁸Ga-PSMA-617	<ul style="list-style-type: none"> • Improved binding affinity. • Increased internalization into PCa cells vs ⁶⁸Ga-PSMA-11. • PSMA-617 can be chelated with ¹⁷⁷Lu to enable pure theranostic pairs. • Companion agent (¹⁷⁷Lu-PSMA-617) is widely used and extensively researched. 	<ul style="list-style-type: none"> • More research is necessary to evaluate use across multiple clinical settings. 	—
¹⁸F-DCFPyl	<ul style="list-style-type: none"> • Extensively researched; labeling with ¹⁸F leads to commercialization. • Longer half-life and shorter position range leads to better image quality. • Lower hepatic background; may be advantageous in later stages of PCa. 	<ul style="list-style-type: none"> • High uptake in the urinary system can lead to challenges in detecting small lymph nodes in pelvis. 	Received FDA approval.
¹⁸F-PSMA-1007	<ul style="list-style-type: none"> • Reduced urinary clearance offers elective assessment of the prostate. 	<ul style="list-style-type: none"> • Higher detection of benign lesions vs ⁶⁸Ga-PSMA-11. • Higher uptake in liver makes it difficult to identify liver lesions. 	—
¹⁸F-rhPSMA-7	<ul style="list-style-type: none"> • Radiohybrid ligand allows for rapid labeling and pure imaging of theranostic pairs. • Rapid blood clearance; low urinary excretion. 	<ul style="list-style-type: none"> • Uptake in bones, healing fractures, and degenerative changes not attributed to PCa can lead to false positives. • More research is necessary to evaluate agent in multiple clinical settings. 	Trials underway: NCT04186819 and NCT04186845
CTT1057	<ul style="list-style-type: none"> • Similar biodistribution to urea backbone drugs with lower dose to kidneys and salivary glands • Companion therapeutic agent (CTT1403) is currently in clinical trials 	<ul style="list-style-type: none"> • More research is necessary to evaluate use of this agent in multiple clinical settings 	Phase 1 trial completed
⁶⁴Cu-PSMA-617	<ul style="list-style-type: none"> • Enables delayed imaging (up to 17 h postinjection). • Easier to transport to remote facilities. 	<ul style="list-style-type: none"> • Potentially higher radiation exposure. • More research is necessary to evaluate ⁶⁴Cu-based imaging agents alongside ¹⁸F- and ⁶⁸Ga-based imaging agents. 	—

PCa, prostate cancer; PSMA, prostate-specific membrane antigen; UCLA, University of California, Los Angeles; UCSF, University of California, San Francisco.

imaging is negative and the PSA level is up, that does not mean that there is no micrometastatic disease. One cannot just 100% believe the negative imaging. There is cancer activity that has to be managed based on evidence-based standards of care and clinical judgment.

Detecting recurrence and treating metastatic disease are key challenges in prostate cancer.³ Conventional imaging modalities struggle with early detection, and hormone-resistant tumors pose a major clinical hurdle. As PSMA is often overexpressed in prostate cancer, PSMA-targeting molecules are being developed to detect early progression and to treat mCRPC. Due to uptake of ligand-binding PSMA into tumor cells, a high-quality image is generated. **Table 1** presents several emerging PSMA-targeting molecules currently used and under development to detect and treat prostate cancer.⁴

Q / Where do you see the field of prostate cancer going in the next 5 years?

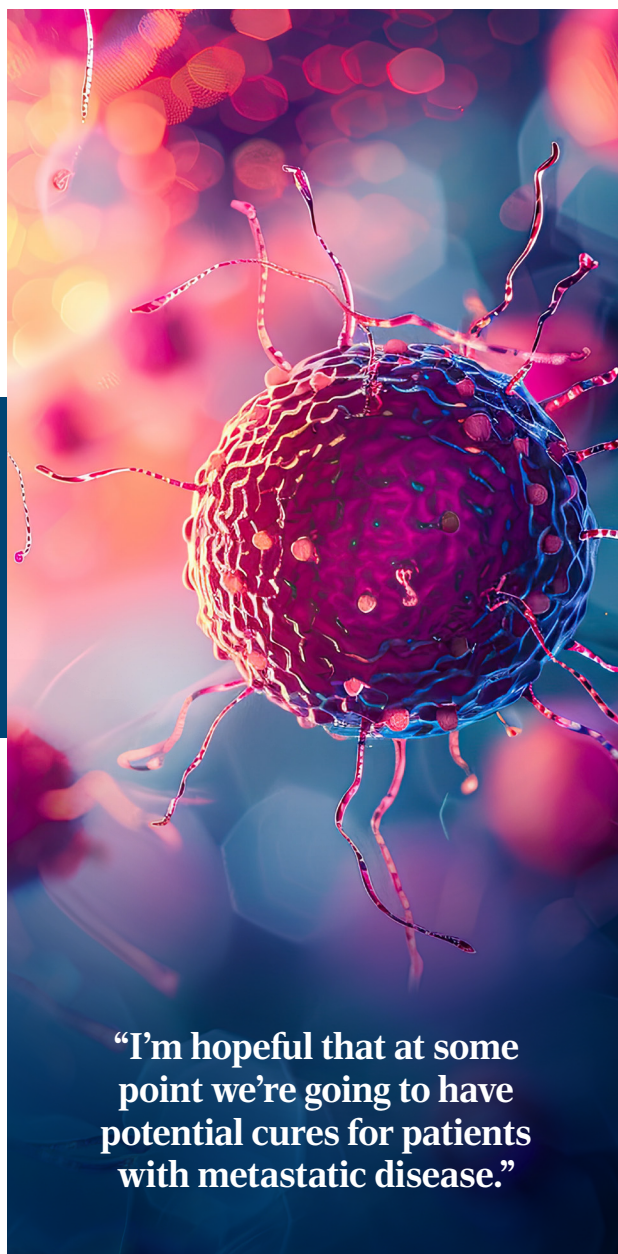
HUSSAIN / Basically, the field is moving in a wonderful way with significant investment at all levels regarding research, science, clinical trials, and enrollment in different parts of the world, not just in Western countries. I think we are moving toward converting prostate cancer, when it comes to metastatic disease, from an imminently deadly disease to more of a chronic disease.

When I entered the field 3 decades ago, the median survival for men with metastatic hormone-sensitive disease was roughly 2.5 to 3 years. Now, it has doubled to nearly 6 years with a significant number of men living beyond 10 years. In fact, my practice includes several patients who have surpassed the 10-year mark since their initial diagnosis of metastatic hormone-sensitive disease.

We've seen similar progress in castration-resistant disease. The median survival was about 9 months when I started my clinical practice, but that has extended considerably. We've made substantial strides, and I'm optimistic that we're moving closer to managing this as a chronic disease with the ultimate goal of finding a cure. ■

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