Evolving Role of Prostate-Specific Membrane Antigen-Positron Emission Tomography in Metastatic Hormone-Sensitive Prostate Cancer: More Questions than Answers?

Maha Hussain, MD[1]; Michael A. Carducci, MD[2]; Noel Clarke, MBBS[3]; Sarah E. Fenton, MD, PhD[1]; Karim Fizazi, MD, PhD[4]; Silke Gillessen, MD, PhD[5,6,7]; Heather Jacene, MD[8]; Michael J. Morris, MD[9]; Fred Saad, MD[10]; Oliver Sartor, MD[11]; Mary-Ellen Taplin, MD[12]; Neha Vapiwala, MD[13]; Scott Williams, MD[14]; and Christopher Sweeney, MD[12]

Although most men with metastatic hormone-sensitive prostate cancer (mHSPC) die of prostate cancer (PCa), there remains significant outcome variability, with approximately 18.5% living 10 years or longer.[1] Prognosis and management are determined in part by disease extent detected on conventional imaging (CIM; ^{99m}Tc Bone and computed tomography [CT] scan; Data Supplement, online only). With the advent of multiple new life-prolonging therapies, clinicians can better personalize therapy on the basis of these findings. However, the availability of new imaging modalities with varying performance characteristics has added more variables that affect clinical decision making.

Prostate-Specific Membrane Antigen (PSMA)-positron emission tomography (PET) is a more sensitive imaging tool compared with CIM, detecting previously CIM-invisible disease (micrometastases).[2,3] PET radiotracers and PSMA-PET development are discussed in the Data Supplement. Several trials demonstrated that PSMA-PET imaging resulted in management changes;[4-6] however, all available clinical trial data guiding the treatment of patients with mHSPC are CIM-based. Integrating PSMA-PET into clinical practice without prospective evidence derived from clinical trials poses significant challenges. In this Comments and Controversy paper, we detail what is known and what remains to be determined for optimal implementation of PSMA-PET imaging and provide opinions generated by an international, multidisciplinary group of PCa experts to help guide decision making until further data are available.

Potential Pitfalls

Both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL (now ^{18}F-piflufolastat, Pylarify [Progenics Pharmaceuticals, North Billerica, MA]) are widely available and are US Food and Drug Administration–approved for the staging of newly diagnosed high-risk PCa and for detecting disease at biochemical recurrence (BCR).[2,3] Studies supporting the improved sensitivity and specificity of PSMA-PET are detailed in the Data Supplement. Although better staging is intuitively more desirable for therapeutic planning, transformative technology like PSMA-PET has progressed at a pace that far outstrips our ability to perform trials to define how best to use PSMA-PET imaging with clinically meaningful end points, which require years or even decades to mature.

PSMA-PET is in essence a *different* biomarker compared with CIM. Similar to other imaging modalities, as we begin to learn more about PSMA-PET, there are anecdotal reports of false positivity as a biopsy of PSMA-positive area revealed a benign finding or malignancy other than PCa.[7] Thus, it is critical to carefully integrate PSMA-PET into the staging of patients, so we are not misguided by false positives or false negatives.

Another area of concern is changing the prognosis and management of previously defined risk categories. The Prostate Cancer Working Group 2 and 3 model defined clinical subgroups based partly on disease detection by CIM.[8,9] With the increased sensitivity of molecular imaging, these classifications will potentially be redefined. In addition, the prognosis of each defined disease class will change, as the highest-risk patients of early clinical subgroups will likely be recategorized into the subsequent clinical stage, creating the well-known Will Rogers' effect.[10] Although identification of a patient's true disease extent is critical to developing a comprehensive and rational treatment plan, appreciating that extent and what to do about it are entirely different issues.

To that end, this shift in disease state may have cascading effects on management strategies. Some examples of concerns specifically related to these changes include the following:

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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1. Patients with BCR may be exposed to the risks of overtreatment after upstaging without known survival benefits, resulting in possible quality-of-life (QOL) declines because of the earlier and longer-term use of more potent and potentially toxic therapies.
2. By default, patients with high-risk newly diagnosed disease are very likely to have micrometastases and many patients with this clinical picture were included in trials where systemic + local therapy imparted OS benefit over radiation alone.[11-13] Patients with low-volume mHSPC also benefit from treatment of the primary tumor.[14] Upstaging may deny a patient potentially curative or life-prolonging primary or salvage combination therapy.[15,16]
3. Despite the sensitivity of PSMA-PET, micrometastases below the detection ability of this study will still be missed. Thus, potentially curative adjuvant therapy should not be withheld based on a negative PSMA-PET.
4. Patients with nonmetastatic castration-resistant PCa (CRPC) upstaged on molecular imaging may be treated with the full armamentarium of drugs applicable to metastatic CRPC without data supporting the benefit of this choice.

Further Questions to Investigate

With the high confidence in imaging accuracy and documented evidence that it is dramatically altering management, it is imperative that PSMA-based imaging is evaluated beyond simple biomarker performance measures. There are several areas where this evaluation is critical to determine its clinical value. Although desirable, the ability to perform randomized trials that include a no PET option is being rapidly curtailed because of widespread availability of PSMA-PET. Fortunately, several studies are currently underway. PATRON (ClinicalTrials.gov identifier: NCT04557501) aims to guide therapy by randomly assigning men referred for radiotherapy in the primary or recurrence setting to CIM or PSMA-PET/CT. Comparing ^{18}F-fluciclovine with ^{68}Ga-PSMA PET, the EMPIRE-2 study is recruiting patients to compare two radiotracers (ClinicalTrials.gov identifier: NCT0376259). In addition, the INDICATE trial (ClinicalTrials.gov identifier: NCT04423211) is currently adding PSMA-PET as an option for baseline imaging. Such studies will provide a better understanding of how increased imaging sensitivity affects diagnosis and hopefully clinical outcomes. Studies also aim to address the use of metastasis-directed therapy to PSMA-positive areas for men with oligometastatic disease to delay time to progression using various biomarkers/imaging (ClinicalTrials.gov identifier: NCT04983095).

Although focusing on treatment intensification to improve outcomes is a widely shared goal, it is important to remember that the risk-benefit ratio is crucial given the lack of data supporting the clinical benefit of applying traditional treatment paradigms to non-CIM findings. Furthermore, many patients with PSA relapse after local therapy with PSMA-PET–positive disease and no metastases by CIM will be elderly or infirm and potentially could be managed for many years with surveillance. In this population, treatment intensification may compromise QOL and general health. Designing trials that incorporate QOL end points will be key to assessing the true treatment value of these clinical decisions.

There is much to be learned about the natural history of PSMA-PET–positive lesions, and the kinetics of change after therapy are not well described. Understanding the clinical meaning of both response and progression is clearly a top priority.

Another area of active investigation is the use of PSMA-PET positivity as a biomarker for treatment selection using PSMA-targeted therapies in mHSPC (ClinicalTrials.gov identifiers: NCT04443062 and NCT03511664). The predictive value of baseline PSMA-PET imaging as a biomarker for clinical benefit using ^{177}Lu-PSMA-617 in this population has not yet been established, and its role as a post-treatment response or progression indicator has not been formally tested. Further prospective trials are needed to address these questions.

The Future: Conclusion and Recommendations

Given the widespread introduction of PSMA-PET imaging and lack of prospective trial data clearly directing a clinician's decision making, we assembled this international multidisciplinary group of PCa experts to provide an expert

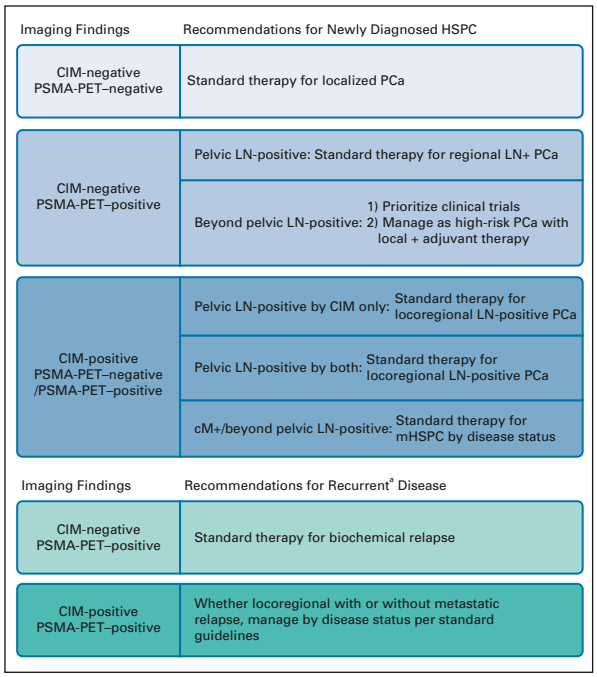

FIG 1. Management recommendations on the basis of the findings of CIM and PSMA-PET. [a]Metachronous. CIM, conventional imaging; HSPC, hormone-sensitive prostate cancer; LN, lymph node; mHSPC, metastatic hormone-sensitive prostate cancer; PCa, prostate cancer; PSMA-PET, prostate-specific membrane antigen-positron emission tomography.

opinion regarding the appropriate implementation of PSMA-PET in daily practice pending prospective trials data. Recommendations are outlined in Figure 1.

Ideally, novel imaging will improve patient care by increasing the ability to detect early metastases, hence better personalizing curative-intent therapy, accelerating early clinical trial development, and more rapidly determining response and resistance to treatment. PSMA-PET is swiftly becoming available in practices internationally, and thus, limiting its use would be like turning back the tide. However, it is critical to remember that imaging is a clinical tool and that management is a clinical decision, integrating data and clinical judgment. It is the responsibility of clinicians to apply the imaging findings for their patients' benefit. If the imaging findings are not consistent with other clinical characteristics, it is important to discuss this with the interpreting physician and consider biopsy and/or close monitoring to better assess the disease and inform the treatment plan. In addition, as knowledge regarding this imaging is still incomplete, it is good practice to let patients know before obtaining the imaging that there are many scenarios where management is not supported by data.

Outside clinical trials, our shared recommendation is that there is little utility currently for the routine use of PSMA-PET in patients with detectable metastases on CIM and recommendations regarding therapy should be based on CIM findings. For those with a newly diagnosed PCa who do not have systemic metastatic disease on CIM, therapy should be based on curative-intent standards of care whether disease on PSMA-PET remains localized to regional lymph nodes or extends to disease outside of the pelvis. Until data provide better guidance, if a PSMA-PET/CT is obtained, we advise clinicians to base treatment decisions on the extent of disease seen on CIM. Data from previous trials using CIM will stand on their own merits. One may argue the merits of disease reclassification, but conjectural hypotheses will never be proven or disproven using trials that did not prospectively include PSMA-PET imaging.

AFFILIATIONS

[1]Robert H Lurie Comprehensive Cancer Center, Division of Hematology/Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL
[2]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
[3]The Christie and Salford Royal Hospitals, Manchester University, Manchester, England
[4]Institut Gustave Roussy, University of Paris Saclay, Paris, France
[5]Oncology Institute of Southern Switzerland, Università della Svizzera Italiana, Bellinzona, Switzerland
[6]University of Bern, Division of Cancer Sciences, Bern, Switzerland
[7]University of Manchester, Manchester, England
[8]Dana-Farber Cancer Institute/Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[9]Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY
[10]Division of Urology and GU Oncology, Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, Quebec, Canada
[11]Tulane Cancer Center, Tulane Medical School, New Orleans, LA
[12]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA
[13]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
[14]Peter MacCalllum Cancer Center and University of Melbourne, Melbourne, Australia

CORRESPONDING AUTHOR

Maha Hussain, MD, Robert H Lurie Medical Research Center, 303 E. Superior St, Suite 3-107, Chicago, IL 60611;
e-mail: maha.hussain@northwestern.edu.

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AUTHOR CONTRIBUTIONS

Conception and design: Maha Hussain, Christopher Sweeney
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Maha Hussain
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Michael A. Carducci

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Consulting or Advisory Role: Roche/Genentech, Pfizer, Exelixis
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Noel Clarke
Honoraria: Janssen-Cilag, Astellas Pharma, Sanofi, Bayer, AstraZeneca, Ferring, Ipsen
Consulting or Advisory Role: Astellas Pharma, Janssen-Cilag, Ferring, Bayer, Sanofi
Speakers' Bureau: Janssen-Cilag, Janssen-Cilag, Astellas Pharma, Astellas Pharma, AstraZeneca
Research Funding: AstraZeneca (Inst), AstraZeneca
Travel, Accommodations, Expenses: Janssen-Cilag, Astellas Pharma, Sanofi, Bayer, AstraZeneca, Ferring, Ipsen

Karim Fizazi
Honoraria: Janssen (Inst), Sanofi (Inst), Astellas Pharma (Inst), Bayer (Inst)
Consulting or Advisory Role: Janssen Oncology (Inst), Bayer, Astellas Pharma (Inst), Sanofi (Inst), Orion, AstraZeneca (Inst), ESSA (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Clovis Oncology (Inst), Novartis (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Janssen, MSD, AstraZeneca

Silke Gillessen
Consulting or Advisory Role: Astellas Pharma (Inst), Janssen (Inst), Bayer (Inst), Orion, Tolero Pharmaceuticals (Inst), MSD Oncology (Inst), Roche (Inst), Amgen, Pfizer (Inst), BMS (Inst), Telix Pharmaceuticals (Inst), MSD Oncology, AAA HealthCare (Inst), Orion (Inst), Amgen (Inst)
Patents, Royalties, Other Intellectual Property: Method for biomarker (WO 3752009138392 A1)
Travel, Accommodations, Expenses: ProteoMediX
Other Relationship: ProteoMediX, Aranda Pharma (Inst), Menarini Silicon Biosystems (Inst)

Heather Jacene
Honoraria: Blue Earth Diagnostics
Consulting or Advisory Role: Advanced Accelerator Applications, Spectrum Dynamics
Research Funding: GTx (Inst), Siemens Healthineers (Inst), Blue Earth Diagnostics (Inst)
Travel, Accommodations, Expenses: GE Healthcare

Michael J. Morris
Stock and Other Ownership Interests: Doximity
Consulting or Advisory Role: Bayer, Endocyte, Advanced Accelerator Applications, ORIC Pharmaceuticals, Johnson & Johnson, Curium Pharma, Athenex, Novartis, NCCN, Progenics, Exelixis, Lantheus Medical Imaging
Research Funding: Bayer (Inst), Sanofi (Inst), Endocyte (Inst), Progenics (Inst), Corcept Therapeutics (Inst), Roche/Genentech (Inst), Janssen (Inst)
Travel, Accommodations, Expenses: Endocyte, Fujifilm

Fred Saad
Honoraria: Astellas Pharma, Janssen Oncology, Sanofi, Bayer, AstraZeneca, AbbVie, Myovant Sciences, Pfizer, BMS, Novartis, Advanced Accelerator Applications, Merck, Knight Therapeutics
Consulting or Advisory Role: Astellas Pharma, Janssen Oncology, Sanofi, AstraZeneca/MedImmune, Bayer, Pfizer, Myovant Sciences, AbbVie, Novartis, Advanced Accelerator Applications, Knight Therapeutics
Research Funding: Astellas Pharma (Inst), Bayer (Inst), Janssen Oncology (Inst), Sanofi (Inst), AstraZeneca (Inst), Pfizer (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Advanced Accelerator Applications (Inst), Merck (Inst)

Oliver Sartor
Stock and Other Ownership Interests: Lilly, GlaxoSmithKline, AbbVie, Cardinal Health, United Health Group, PSMA Therapeutics, Clarity Pharmaceuticals, Noria Therapeutics, Clovis Oncology
Consulting or Advisory Role: Bayer, Sanofi, AstraZeneca, Dendreon, Constellation Pharmaceuticals, Advanced Accelerator Applications, Pfizer, Bristol Myers Squibb, Bavarian Nordic, EMD Serono, Astellas Pharma, Progenics, Blue Earth Diagnostics, Myovant Sciences, Myriad Genetics, Novartis, Clarity Pharmaceuticals, Fusion Pharmaceuticals, Isotopen Technologien, Janssen, Noxopharm, Clovis Oncology, Noria Therapeutics, Point Biopharma, TeneoBio, Telix Pharmaceuticals, Theragnostics
Research Funding: Bayer (Inst), Sanofi (Inst), Endocyte (Inst), Merck (Inst), Invitae (Inst), Constellation Pharmaceuticals (Inst), Advanced Accelerator Applications (Inst), AstraZeneca (Inst), Dendreon (Inst), SOTIO, Janssen, Progenics, Amgen (Inst), Lantheus (Inst)
Patents, Royalties, Other Intellectual Property: Koochekpour, Sartor AO, inventors. Saposin C and receptors as targets for treatment of benign and malignant disorders. US patent awarded January 23, 2007 (patent No. 7,166,691)
Expert Testimony: Sanofi
Travel, Accommodations, Expenses: Bayer, Johnson & Johnson, Sanofi, AstraZeneca, Progenics

Mary-Ellen Taplin
Honoraria: Janssen-Ortho, Clovis Oncology, Astellas Pharma, Incyte, UpToDate, Research to Practice, Pfizer, Bayer, Amgen, AstraZeneca, Progenics, Guidepoint Global, Celgene, Merck, GlaxoSmithKline, Myovant Sciences, Roivant, Pfizer, AbbVie, Arcus Biosciences, Constellation Pharmaceuticals
Consulting or Advisory Role: Janssen-Ortho, Bayer, Guidepoint Global, Best Doctors, Inc, UpToDate, Clovis Oncology, Research to Practice, Myovant Sciences, Incyte, Pfizer, AstraZeneca, Arcus Ventures
Research Funding: Janssen-Ortho (Inst), Medivation (Inst), Bayer (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Medivation, Janssen Oncology, Tokai Pharmaceuticals, Astellas Pharma, Incyte, Pfizer, Clovis Oncology, Bayer

Neha Vapiwala

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Scott Williams
Consulting or Advisory Role: Amgen, Janssen (Inst)
Travel, Accommodations, Expenses: Astellas Pharma

Christopher Sweeney
Stock and Other Ownership Interests: Leuchemix
Consulting or Advisory Role: Sanofi, Janssen Biotech, Astellas Pharma, Bayer, Genentech/Roche, AstraZeneca, Pfizer, Amgen, Lilly
Research Funding: Janssen Biotech (Inst), Astellas Pharma (Inst), Sanofi (Inst), Bayer (Inst), Dendreon, Pfizer (Inst)
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