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A Clinician's Guide to Targeted Precision Imaging in Patients With Prostate Cancer (RADAR VI)

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Purpose: The advent of new imaging agents offers enhanced sensitivity and specificity in the detection and staging of prostate cancer. A growing array of treatment options and ongoing advancements in imaging technologies allow earlier and more extensive detection of metastatic disease and shifting the boundaries between disease states previously defined by conventional imaging. This review seeks to synthesize existing data and expert opinion to better guide patient management in the new era of targeted precision imaging (TPI).

Materials and Methods: The Radiographic Assessments for Detection of Advanced Recurrence VI Group gathered to develop pathways/recommendations regarding how TPI could best be deployed, given approvals of key radiotracers including ^{18}F-fluciclovine, ^{68}Ga-PSMA, and ^{18}F-DCFPyL positron emission tomography/CT.

Results: Radiographic Assessments for Detection of Advanced Recurrence VI Group members developed consensus pathways/suggestions based on the best available evidence for use of TPI in prostate cancer.

Conclusions: Patients with prostate cancer have the potential to benefit from judicious use of TPI. However, additional research is needed to ensure that TPI is used appropriately and provides actionable findings that inform treatment decisions for these patients.

Key Words: clinical decision-making, diagnostic imaging, neoplasm metastasis, practice guideline, prostatic neoplasms

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PROSTATE cancer (PCa) remains the most common noncutaneous cancer in men, accounting for a projected 268,490 new cases and 34,500 deaths in the United States in 2022.[1] Although curable if diagnosed early, 30% to 40% of patients will experience biochemical recurrence (BCR) after initial local treatment.[2] Given that treatment goals and options differ along the continuum from localized to recurrent to metastatic castration-resistant prostate cancer (mCRPC), accurately identifying the presence and extent of metastatic disease is critical to providing the best possible advice for treatment and prognosis. Toward this goal, recently approved positron emission tomography (PET) radiotracers seem to offer superior sensitivity and specificity relative to conventional imaging (CI), namely CT and bone scans. However, whether gains in sensitivity and specificity translate to meaningful improvements in clinical outcomes remains unclear. Indeed, advances in imaging have outpaced clinical trials in PCa, leaving an absence of level I data to direct decision-making.

Against the backdrop of evolving imaging technologies and limited clinical data, clinicians increasingly require guidance to ensure their appropriate application in cases where clinically meaningful improvements are possible. Since 2014, the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group has provided consensus recommendations on key questions such as the optimal timing of CI (RADAR I) and use of next-generation technologies (RADAR III) to facilitate early detection of metastases.[3,4]

METHODS

In response to recent practice-changing advances—notably the emergence of prostate-specific membrane antigen (PSMA) PET imaging—RADAR reconvened as RADAR VI with additional experts across 4 subcommittees: biochemical failure, newly diagnosed disease, nonmetastatic castrate-resistant prostate cancer, and castrate-resistant disease. Members of the 4 RADAR VI subcommittees individually reviewed available publications and presentations and then convened in November 2021 to discuss the optimum use of new imaging modalities. Committee members considered the expanding array of approved and investigational radiotracers, their commercial availability, and how these factors would affect equitable care across the full spectrum of practice settings, from community and rural locations to academic, urban, and tertiary referral centers. Central to these discussions was the patient experience—whether, why, when, and how to present targeted precision imaging (TPI) options to appropriately selected men with PCa.

RADAR VI experts discussed the latest relevant data, highlighting not only potential advances offered by state-of-the-art imaging modalities but also the limitations of these modalities. In this regard, the committee sought to balance physicians' need for practical guidance with the challenge of making recommendations in areas where level I data are scarce and gray areas in clinical practice remain. In addition, the committee considered existing guidelines, where available, and how best to refine nomenclature to keep pace with the rapidly evolving field of PCa imaging technologies.

Far from a static document, RADAR VI's best-practice/appropriate-use pathways for TPI are expected to evolve as more definitive clinical trials are completed and long-term outcomes become available. The following suggestions update several RADAR III specifics while often underscoring the potential value of earlier treatment initiation in improving clinical outcomes.

RESULTS

CI Techniques

The National Comprehensive Cancer Network (NCCN) and others have long recommended bone scintigraphy and CT for staging PCa and evaluating response to treatment.[5,6] However, limitations of these technologies are well-known. Although bone scintigraphy is widely available and identifies bone lesions fairly effectively, it is rarely positive in early, asymptomatic disease or in recurrent patients with low PSA levels.[5,7] CT rarely detects recurrent tumors in the surgical bed, and its reliance on nodal size for evaluation confers poor sensitivity.[7]

Nomenclature Change: TPI

The goal of early detection and treatment of PCa is to forestall progression to advanced/metastatic disease and the attendant need for systemic therapies. Previously, authors including those of RADAR III collectively referred to novel radiotracers under investigation for PCa diagnosis (and sometimes treatment) as next-generation imaging (NGI). With multiple such agents now Food and Drug Administration (FDA)-approved, these agents no longer represent the next generation. Indeed, these technologies have arrived, presenting both opportunities and challenges. Henceforth, RADAR VI recommendations will refer to them as targeted precision imaging or TPI. The term TPI goes beyond PSMA; some RADAR VI recommendations name PSMA specifically, but additional radiopharmaceuticals are available or under development. Emerging theranostics, with radioligands linked to PSMA-targeted antibodies or small molecules, may lead to dual theranostic/TPI hybrids. It is important for physicians and stakeholders to adopt the new terminology for consistency and clarity from clinical usage to claims databases.

TPI agents rank among the most significant discoveries to affect the diagnosis and treatment of localized and advanced PCa. Although not detecting microscopic disease, these technologies locate disease earlier than CI.[8] In the randomized proPSMA study, PSMA PET-CT compared with CI demonstrated greater

Table 1. *Advantages, Disadvantages, and Status of Select PSMA-Targeting PET Radiotracers*[33]

Name of radiotracer	Advantages	Disadvantages	Status
^{68}Ga-PSMA-11	• Extensively researched • Lower uptake time • Lower radiation exposure • TLX591-CDx radiopharmaceutical cold kits will enable greater accessibility	• ^{68}Ga generator-dependent production makes mass production challenging relative to ^{18}F-based agents • Shorter half-life makes transportation to remote facilities difficult	FDA-approved (initially covered only UCSF and UCLA; since expanded)
^{68}Ga-PSMA-617	• Improved binding affinity and increased internalization into PCa cells compared with ^{68}Ga-PSMA-11; PCa lesions shown with high contrast • PSMA-617 can be chelated with ^{177}Lu, enabling pure theranostic pairs • Companion theranostic agent (^{177}Lu-PSMA-617) FDA-approved and extensively researched	• Further research across clinical settings is needed	FDA-approved
^{18}F-DCFPyL	• Extensively researched • Labeling with ^{18}F leads to easier commercialization • Longer half-life and shorter positron range may lead to better image quality and distribution • Lower hepatic background may be advantageous in later stages of PCa	• High uptake in the urinary system can lead to challenges in detecting small lymph nodes in pelvis	FDA-approved
^{18}F-PSMA-1007	• Reduced urinary clearance offers effective assessment of the prostate	• Higher detection of benign lesions compared with ^{68}Ga-PSMA-11 • Higher uptake in liver makes it difficult to identify liver lesions	Trials underway (NCT04487847)
^{18}F-rhPSMA-7.3	• The radiohybrid ligand allows for rapid labeling and pure imaging or theranostic pairs • Rapid blood clearance, low urinary excretion	• Uptake in bones, healing fractures, and degenerative changes not attributed to PCa can lead to false positives • Further research needed	Trials underway (NCT04186819, NCT04186845)
^{18}F-CTT1057	• Based on a phosphoramidate scaffold that irreversibly binds to PSMA, shown to have similar biodistribution to urea backbone drugs with lower dose to kidneys and salivary glands • Companion therapeutic agent (CTT1403) is currently in clinical trials (NCT03822871)	• Further research needed	Trials underway (NCT04838613, NCT04838626)
^{64}Cu-PSMA-617	• Enables delayed imaging (up to 17 h after injection), easier to transport to remote facilities	• Potentially higher radiation exposure • Further research needed	Trials underway (NCT04868604)

^{18}F-DCFPyL, 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid; FDA, Food and Drug Administration; PCa, prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
Derived and adapted from Murthy et al.[33]

accuracy (92% vs 65%; $P < .0001$), sensitivity (85% vs 38%), and specificity (98% vs 91%) in men with high-risk PCa before curative-intent surgery or radiotherapy.[9] Several types of molecular imaging probes in clinical use or under evaluation exploit unique biologic aspects of prostate carcinogenesis by targeting PSMA cell surface proteins; less-specific targets include increased cell metabolism (eg, ^{11}C-acetate, ^{18}F-fluciclovine) or bone matrix adjacent to bone metastases (eg, ^{18}F-NaF).[10] PSMA is overexpressed 100-fold to 1,000-fold on PCa cells, allowing the uptake of ligand-binding PSMA on tumor cells to provide high-quality image.[8]

Table 1 summarizes key FDA-approved TPI radiotracers in prostate cancer. Presently, the most widely used radiotracers for PET imaging incorporate fluorine or gallium agents that have particularly advanced the utility and accessibility of PET (see online supplement for a review of data supporting the use of radiotracers for TPI, including a comparison of radiotracer characteristics [Supplementary Table I, http://links.lww.com/JU9/A0] and relative uptake of ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL in target organs [Supplementary Table II, http://links.lww.com/JU9/A0]).

GENERAL PRINCIPLES

RADAR VI offers practical suggestions in key patient groups based largely on 1 critical question: *What is the goal of imaging in each group?* Distinguishing between localized and metastatic PCa—ie, potentially curable vs presumed incurable disease—represents perhaps the most profound use of TPI. Other important clinical goals include differentiating between lower-volume and higher-volume disease and determining eligibility for therapy guided by PSMA or other emerging biomarkers. In addition, TPI can provide a more sensitive tool for defining response to treatment, particularly with oligometastatic disease. As treatment options continue to expand, particularly in the setting of hormone-sensitive prostate cancer, there is a need to identify patients who may benefit from therapy escalation and/or metastasis-directed therapy (MDT).

Decisions about when, how, and how often to perform TPI depend on goals inherent to each disease state. Detecting curable disease dictates choosing a definitive therapy, whereas high-volume vs low-volume metastases—historically defined by bone scan results, which are not easily extrapolated to PSMA

Table 2. *General Principles for Prostate Cancer Imaging*

1. Discuss the risks and benefits of TPI with the patient.
2. Consider pretreatment imaging followed by periodic monitoring.
   - Before initiating ADT, consider performing baseline scans with CI.
   - Imaging at least yearly is reasonable for patients treated with ADT and more frequently for those receiving intermittent therapy.
   - Imaging intervals differ based on aggressiveness of the disease state. Consider more frequent imaging in the event of a PSA rise or appearance of symptoms.
3. Consider clinical symptoms, PSA, and radiographic assessment in treatment decisions; together, these provide meaningful and comprehensive guideposts for management.
4. When considering TPI, RADAR VI suggestions largely omit specific numerical thresholds (for PSA and other treatment parameters). This was done purposefully to maximize clinicians' freedom to select a pathway tailored to each patient individually.
5. TPI data should be actionable. Avoid scenarios where results are unlikely to affect treatment decisions.

ADT, androgen deprivation therapy; CI, conventional imaging; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; TPI, targeted precision imaging.

imaging—demand their own treatment strategies. When considering the best available evidence and relying on expert consensus on where data are lacking, clinicians should keep in mind several general principles applicable to all disease states (Table 2).

DISCUSSION

Newly Diagnosed Prostate Cancer

In keeping with approvals of the most recent PSMA agents, NCCN recommends the use of these agents in high-risk localized disease and initial or subsequent BCR.[5] RADAR III recommended considering NGI (^{18}F-fluciclovine [^{18}F-FACBC] or PSMA-targeted PET/CT) for newly diagnosed patients in whom CI is equivocal or negative and suspicion for metastatic disease remains high. RADAR VI appropriate use criteria address anticipated clinical scenarios in greater detail (Table 3).

The present recommendations largely mirror those of the NCCN and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).[5,11] The latter deem PSMA-PET appropriate for newly diagnosed unfavorable intermediate-risk, high-risk, or very high-risk PCa and for such cancers with negative/equivocal findings or oligometastatic disease on CI.

Consistent with NCCN guidelines, we do not consider negative CI a pre-requisite for TPI. TPI can replace CI in many cases, such as those involving low PSA levels, where TPI is far more accurate. For men with apparent high-risk local disease and negative CI, TPI can provide more detail regarding potential spread of disease. Additional considerations are summarized in Table 4.

Biochemical Relapse

Table 5 summarizes recommendations for imaging for BCR. RADAR III recommended considering TPI for men with BCR and PSA $\geq$0.5 ng/dL, and if PSA $<$0.5, based on the performance of specific TPI techniques. RADAR VI suggests considering TPI in patients with rising PSA at or above 0.2 ng/dL who may benefit from further MDT and those with rising PSA who do not yet meet the Phoenix criteria.[12] Current guidelines also suggest considering PET with novel radiotracers as an alternative to or after negative CI in men with BCR.[6]

Any discussion of BCR must include the classic definitions based on PSA of nadir + 0.2 ng (after RP)[13] and nadir + 2 ng (after radiotherapy [RT], high-intensity focused ultrasound, or cryotherapy).[14] Whereas the former is still used in urology, use of the latter is waning in radiation oncology. Although practice patterns vary, radiation oncologists concerned about confirmed rising PSA, regardless of absolute value, may choose not to wait for a 2-point rise above nadir before imaging; this approach is consistent with SNMMI guidelines, which do not specify numerical cutoffs for post-RP or post-RT PSA increases.[11]

To date, most TPI studies have occurred in the BCR setting. The strongest evidence that TPI can act as a radio-biomarker for such patients comes from the phase 2/3 EMPIRE-1 trial, which sets the paradigm for

Table 3. *Imaging for Newly Diagnosed PCa*

RADAR I CI recommendations	CI in patients with high-risk and intermediate-risk disease meeting $\geq$2 of the following criteria: • PSA $>$10 ng/dL • Gleason $\geq$7 • Palpable disease ($\geq$T2b)
RADAR III NGI recommendations	If CI is equivocal or negative with continued high suspicion for metastatic disease, consider NGI.
RADAR VI TPI recommendations	• Unfavorable intermediate-risk, high-risk, or very high-risk PCa ± CI[a] • Inconclusive prior CI in which there is a high clinical suspicion of metastatic or locoregional disease or risk of nodal metastasis[b] • Patients who have an elevated molecular marker (Decipher/Oncotype DX/Prolaris) score • Patient populations with genomically/diverse high-risk

CI, conventional imaging; NGI, next-generation imaging; PCa, prostate cancer; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; TPI, targeted precision imaging.

[a] For all patients, negative CI should not be considered a pre-requisite for TPI.

[b] Validated by nomogram.

Table 4. *Additional Considerations for TPI in Newly Diagnosed PCa*

Consideration	Recommendations/commentary
Cost	Payers may require bone scans to be performed before TPI. However, bone scintigraphy offers low sensitivity. For payers, performing more precise imaging will eliminate wasteful expenditures on low-yield technologies.
Inconclusive CI	Patients with inconclusive CI and high suspicion of metastases or locoregional disease represent another group in whom TPI offers higher sensitivity and specificity. Targeting these patients makes sense because clinically, it is common to see patients with very high PSA levels whose cancer cannot be detected with CI.
Genomic risk	• Genomic markers have changed the way physicians think about and treat prostate cancer. Recent Oncotype DX data in unfavorable intermediate PCa show that a GPS above 40 significantly predicts BCR. Although the relationship between genomic risk scores and TPI results is not completely understood, a positive correlation likely exists, but at which specific cutpoint should be used to justify such imaging is not known as yet. • In addressing patients with high genomic risk, we chose phrasing consistent with NCCN guidelines. While addressing racial disparities in PCa is beyond the scope of this article, the higher risk attributed to Black patients seems to stem mainly from lack of access to care (social determinants of disease). • The most compelling data for risk of PCa lethality come from younger patients with DNA mutations (ie, BRCA1, HER2, and germline alterations). However, authors chose not to create a separate category because these patients likely will fall into the above categories.
Very low-risk patients	One group for whom the committee does not recommend TPI is low-risk patients, as defined by the NCCN criteria. With no data on TPI in low-risk patients, it is impossible to say whether such imaging will perform efficiently here.
Low-volume PCa	Another consideration involves the role of TPI in the context of low-volume PCa to determine whether patients have more metastases than CI can detect. Currently, most practitioners consider 4-5 local/regional nodes measuring <2 cm in diameter to be low-volume disease. Such numerical thresholds can spark protracted debate that does not necessarily affect outcomes. Acknowledging the difficulty of establishing specific numerical thresholds for MDT, the committee emphasizes that physicians simply consider the size and location of metastases.
Widespread metastatic disease	For patients with widespread metastatic disease on CI at diagnosis, it remains unclear whether TPI would alter treatment plans. A phase 3 trial investigating ^{177}Lu-PSMA-617 in mHSPC (NCT04720157) may provide valuable insight.
AS	The committee spent considerable time discussing patients on AS. Our expert opinion is that to date, CI, PSA testing, and periodic biopsy have sufficed to detect progression in this low-risk category, with multiparametric MRI playing an emerging role. Use of TPI in AS is an uncharted territory. PSMA-PET/TPI may play a role in selection for focal therapy, but even there its role has not been well-validated.

AS, active surveillance; BCR, biochemical recurrence; CI, conventional imaging; GPS, Genomic Prostate Score; MDT, metastasis-directed therapy; mHSPC, metastatic hormone-sensitive prostate cancer; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; TPI, targeted precision imaging.

image-guided RT after RP. Patients with PCa with detectable PSA after prostatectomy and negative CI (no extrapelvic or bone findings) were randomly assigned 1:1 to radiotherapy (in 1.8 Gy fractions) directed by CI alone or to CI plus ^{18}F-fluciclovine-PET. Radiotherapy decisions were rigidly determined by PET findings:

- Extrapelvic or skeletal uptake: no RT
- Pelvic nodal uptake: RT to pelvis (45-50.4 Gy) plus prostate bed (64.8-70.2 Gy)
- Prostate bed uptake alone or no uptake: RT to prostate bed (64.8-70.2 Gy)

At a median follow-up of 3.52 years, patients with detectable PSA and negative CI who underwent salvage RT guided by ^{18}F-fluciclovine-PET/CT experienced significantly improved BCR-free and persistence-free survival vs patients who underwent CI-guided RT (HR, 2.04; 95% CI, 1.06-3.93; $P = .0327$).[15] Whereas EMPIRE-1 incorporates ^{18}F-fluciclovine-PET rather than PSMA-PET, the ongoing EMPIRE-2 trial will compare PSMA vs ^{18}F-fluciclovine in the same clinical scenario (see online supplement for a review of additional evidence guiding the optimal use of TPI in patients with BCR, including decision-making regarding MDT).

M0 CRPC

Nonmetastatic CRPC, or M0 CRPC, represents the most challenging and controversial disease state addressed by RADAR VI.[5,11] Given that most current therapies approved for M0 CRPC are also approved in the metastatic CRPC setting, the potential impact of TPI on treatment decision-making and clinical outcomes for M0 CRPC requires further exploration in clinical trials.[11]

The most fundamental question underlying the relevance of TPI vs CI in any setting is whether the difference in findings represents a difference in disease biology. The answer, clearly, is that the biology is not altered by the test; any belief to the contrary reflects the clinician's conceptual biases. That said, evolving imaging technologies and their

Table 5. *Imaging for Biochemical Relapse*

RADAR I CI recommendations	• First conventional scan when PSA between 5 and 10 ng/mL • Imaging frequency if negative on previous conventional scan: ○ Second scan when PSA = 20 ng/mL and at every doubling of PSA level thereafter (based on PSA testing every 3 mo)
RADAR III NGI recommendations	• Consider NGI for PSA ≥0.5 ng/mL • PSA <0.5 ng/mL can be considered based on specific performance of various NGI techniques
RADAR VI TPI recommendations	• For the patient for whom MDT may be considered, TPI is preferred over CI • Early and accurate identification of sites of disease can lead to more anatomically directed therapy • Optimizing outcomes can be facilitated by early detection of the site(s) of recurrent disease

CI, conventional imaging; NGI, next-generation imaging; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; TPI, targeted precision imaging.

findings provide visual evidence of a key biologic principle regarding "M0" disease that almost all patients with M0 CRPC, in fact, have metastatic disease and imaging results are simply a function of disease volume and sensitivity of the imaging modality. The distinction between M0 and M1 CRPC does not represent a difference in disease biology, but rather the time point and type of imaging performed. In a retrospective study of 200 patients with CRCP defined as nonmetastatic by CI, 98% were found to have PSMA-positive disease, including 55% who had extrapelvic disease by PSMA-PET.[16]

With minimal biological difference, the practical difference between the M0 and M1 disease states, then, is only the different lists of approved agents available to patients with M0 vs M1 disease in the patients' country, which leads to the second question regarding the impact on treatment decisions. Since the available treatments may differ between M0 disease and M1 disease, for the purposes of facilitating treatment selection within national regulatory paradigms, reducing barriers to access, and accommodating clinician judgment, patient interest is not served by eliminating M0 CRPC as a disease state because doing so would only eliminate treatment options for the patient. Considerations for M0 CRPC are presented in Table 6.

Metastatic CRPC

The critical role of TPI in patient selection and treatment decision-making for mCRPC became clear in 2022 with the approvals of lutetium-177 (^{177}Lu)-PSMA-617, the first radioligand therapy indicated for patients with PSMA PET-positive hormone and chemorefractory mCRCP.[17] Table 7 summarizes the full set of imaging recommendations for mCRPC.

Overall, RADAR VI suggestions focus on forestalling the transition from metastatic hormone-sensitive prostate cancer (mHSPC) to mCRPC, a lethal disease state with a median life expectancy of approximately 3 to 4 years. Treatment recommendations, therefore, reflect the more aggressive therapeutic course required for metastatic disease. Whereas RADAR III recommended considering TPI only when CI is negative and one still suspects progression, RADAR VI suggests TPI for disease detection, for treatment eligibility, and as part of treatment monitoring.

The suggested imaging strategy emphasizes consistent timing and technology. It is all too common to see patients who have not been scanned in years and across multiple lines of therapy. Scanning patients at regular intervals (with either CI or TPI) provides a more accurate clinical picture than monitoring with PSA alone or imaging only with PSA progression. PCa progression can also occur without PSA rise.[18] In the ECOG3805 CHAARTED trial, approximately 25% of patients had clinical progression in the absence of confirmed PSA progression and 1 in 8 developed clinical progression with PSA <2 ng/mL. Neuroendocrine dedifferentiation occurs and may explain this phenomenon in some cases.[19]

When performing serial scans, using the same technology as the patient's initial scan is preferred. The radiographic image could look much less favorable on TPI than on technetium-99m methylene diphosphonate/Tc 99m. Without an apples-to-apples comparison, drawing such distinctions is impossible. Whichever technology one chooses, imaging frequency should be a function of expected progression-free survival. For example, a patient who has been on enzalutamide for 5 years is an extreme responder and less frequent imaging may be appropriate.

The flare phenomenon (also called pseudoprogression) typically appears on initial CI scans, although flares can also appear on subsequent scans. On bone and CT scans, radiographic progression or flare may indicate actual disease progression or reflect response to treatment at the disease site.[20,21] Similarly, increased PSMA expression can appear on PET, perhaps as a pharmacodynamic response to treatments such as androgen signaling inhibitors

Table 6. *Imaging for M0 CRPC*

RADAR I CI recommendations	First conventional scan when PSA ≥2 ng/mL Imaging frequency if negative on previous conventional scan: Second conventional scan when PSA = 5 ng/mL and every doubling of PSA thereafter (based on PSA testing every 3 mo)
RADAR III NGI recommendations	Only consider NGI in the setting of PSADT <6 mo when M1 therapies would be appropriate.
RADAR VI TPI recommendations	Appropriate use criteria • TPI is recommended for men with PSA progression while on ADT for BCR if metastasis directed therapy is a potential option. Otherwise, CI can be performed to verify M0 status. • Patients whose disease is detectable only by TPI and not by CI should generally be treated as M0 CRPC because this approach is the most consistent with available level 1 evidence. • Role of TPI while on therapy for M0 CRPC: ○ For patients on systemic therapy for M0 CRPC who had TPI as baseline imaging for their M0 CRPC: □ Imaging should be repeated at least annually and at the time of PSA recurrence. No PSA cutoff for repeat imaging, as yet, because PSMA TPI can be positive even at low PSA levels. ○ For patients treated with local therapy for M0 CRPC who had TPI as baseline imaging for their M0 CRPC: □ TPI may be repeated within 4-6 mo to document the response to therapy and assess for new metastases and then repeated annually as above.

ADT, androgen deprivation therapy; BCR, biochemical recurrence; CI, conventional imaging; CRPC, castration-resistant prostate cancer; NGI, next-generation imaging; PSADT, PSA doubling time; PSMA, prostate-specific membrane antigen; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; TPI, targeted precision imaging.

Table 7. *Imaging for M1 CRPC*

RADAR I CI recommendations	NA
RADAR III NGI recommendations	• Use conventional scans and consider NGI only if conventional scans are negative and the clinician still suspects disease progression • NGI based on at least one of the following: ○ With every doubling of PSA since the previous image ○ Every 6-9 mo in the absence of PSA rise ○ Change in symptomology ○ Change in performance status
RADAR VI CI recommendations	**For detection of M1 CRPC** • In patients with M0 CRPC based on PSADT (PSADT < 10 mo): see M0 CRPC recommendation. • Patients with mHSPC based on symptoms, PSA (rise), and at set frequency (6-12 mo): ○ Scan at least once per year at physician discretion ○ Scans based on symptoms, PSA rise (PSA > 2 or PSADT < 6 mo) **During treatment** • For disease monitoring, to assess response and progressive disease ○ Baseline scans suggested at new treatment start and up to every 12 wk on treatment based on clinical discretion and symptoms **Flare phenomenon** • Flare is not uncommon and can be observed on both bone scan and CT imaging. • The first on-treatment scan is particularly subject to healing flare. • Such scans should be interpreted in the context of clinical symptoms and PSA. Consider TPI only if CI is negative and clinicians still suspects disease progression.
RADAR VI TPI recommendations	**For disease detection** • For initial staging, TPI is recommended for staging of M1 CRPC if it is likely to affect clinical decisions. **For treatment eligibility** • Based on the phase 3 VISION[17] and TheraP[23] trials: ○ PSMA-PET imaging can be used for treatment selection for PSMA-targeted therapies. ○ ^{18}FDG imaging/fluciclovine can be obtained in patients with treatment-refractory M1 CRPC to inform subsequent treatment strategies. **For treatment monitoring** • At present, response criteria are lacking for TPI. TPI should not be used alone to make decisions regarding treatment discontinuation in the context of M1 CRPC.

^{18}FDG, ^{18}fluorodeoxyglucose; CI, conventional imaging; CRPC, castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NGI, next-generation imaging; PSADT, PSA doubling time; PSMA-PET, prostate-specific membrane antigen positron emission tomography; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; TPI, targeted precision imaging.

(eg, apalutamide, darolutamide, enzalutamide).[22] Because PET entered the PCa imaging landscape fairly recently and studies are lacking, the prevalence, prognostic potential, and clinical implications of PSMA "flares" remain unclear.

Because most but not all prostate cancers express PSMA,[8] RADAR VI presents F18-fluciclovine and FDG-PET as options for imaging patients with advanced M1 CRPC. These may provide additional value in identifying PSMA-negative tumors or sites of disease.[23] Aggressive primary tumors (Gleason >7 GG4 or 5) tend toward high FDG uptake.[24] Although high-baseline PSMA uptake may better predict response to Lu-PSMA-617 therapy, high-baseline FDG uptake is generally a poor prognostic marker.[25] FDG-PET is FDA-approved for 3 serial images if providers use the term "subsequent treatment strategy" in documentation. Along with imaging PSMA-negative tumors, F18-fluciclovine and FDG-PET might outperform PSMA-PET for neuroendocrine PCa and aggressive PCa variants defined by either molecular features or immunohistochemistry.[24,26]

Imaging-Discordant (CI$^-$/TPI$^+$) Newly Diagnosed Metastatic PCa

The elevated sensitivity and specificity of TPI have made finding metastatic disease at initial diagnosis increasingly likely. RADAR VI suggests the descriptive term "imaging-discordant newly diagnosed metastatic PCa" (Table 8). As with the conversation about defining M0 vs M1 CRPC, the biology of metastatic PCa is the same regardless of whether it is detectable by CI. What remains lacking is evidence for how such patients should be optimally managed.

Table 8. *Imaging-Discordant (CI$^-$/TPI$^+$) Newly Diagnosed Metastatic PCa*

RADAR I CI recommendations	NA
RADAR III NGI recommendations	NA
RADAR VI TPI recommendations	• TPI is redefining advanced/metastatic prostate cancer. • Men with positive TPI represent a wide spectrum of disease and heterogeneity. • Clinicians have a number of therapeutic agents/interventions available in their armamentarium; most approvals are based on CI. • Earlier therapeutic approaches tend to improve survival and outcomes. • TPI offers an opportunity to implement MDT.

CI, conventional imaging; MDT, metastasis-directed therapy; NGI, next-generation imaging; PCa, prostate cancer; RADAR, Radiographic Assessments for Detection of Advanced Recurrence; TPI, targeted precision imaging.

Table 9. *Criteria for Follow-Up Imaging After Prior Negative/Stable TPI*

Disease state	At diagnosis	Subsequent imaging
BCR (observation or ADT)	X	• At start of treatment • Every 1-2 y thereafter • At PSA doubling • High risk[a] ○ PSADT <6-12 mo ○ Gleason 8-10 ○ Detectable PSA ≤6 mo after definitive treatment ○ Failure to achieve undetectable PSA after definitive treatment • Development of symptoms
nmCRPC	X	• Yearly or • PSADT or • Clinical signs or symptoms
mHSPC	X	• Yearly or • With a rising PSA • Clinical signs or symptoms
mCRPC	X	• Every 12-16 wk[b] • With a rising PSA • Symptoms

ADT, androgen deprivation therapy; BCR, biochemical recurrence; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration-resistant prostate cancer; PSADT, PSA doubling time; TPI, targeted precision imaging.
[a] Consider more frequent imaging for high-risk patients.
[b] For patients in the clinical trial setting.

As predicted in RADAR III, the ability of NGI (TPI) to find more extensive disease than CI is being borne out.[9,27-29] Owing to the heterogeneity of PCa discovered on TPI, therapy is not one-size-fits-all. Whereas most patients are likely to be classified as "low volume" according to definitions based on CI in published mHSPC trials, those with visceral disease by TPI should be considered "high volume." The pitfalls of volume-based definitions notwithstanding, the distinction remains relevant given that treatment selection can vary by disease volume. New therapies approved for mHSPC include abiraterone, enzalutamide, apalutamide, and androgen deprivation therapy (ADT) plus docetaxel; novel regimens such as darolutamide, ADT, and docetaxel set a new standard for a subset of men with mHSPC.[30] For mCRPC, clinicians may choose chemotherapies (docetaxel, cabazitaxel); antiandrogens (abiraterone, enzalutamide); poly (ADP-ribose) polymerase inhibitors (olaparib, rucaparib); and Sipuleucel-T, pembrolizumab, radium 223, and ^{177}Lu-PSMA.

Although data from approval studies performed with CI may not directly correlate with TPI, it seems that however one finds metastases, treatment selection is important, and that earlier aggressive therapies tend to increase survival and outcomes.

Table 10. *Limitations of PSMA*

Domain	Limitations
Tumor heterogeneity	Not all PCa tumors express PSMA[37] (using other radiotracers such as FDG-based PET might find non-PSMA avid lesions).
Limited image resolution	PSMA imaging cannot detect microscopic disease and is no substitute for confirmative histopathology, if an option.[8,33]
Treatment response	Using PSMA-PET to evaluate treatment response is not yet supported by level I evidence. Management based on PSMA-PET/CT has yet to be determined. RECIP 1.0 (Response Criteria in Prostate Cancer) will help establish PSMA PET as a tool for treatment response in the future.[38]
Post-RT accuracy	The sensitivity and specificity of PSMA-PET after RP vs RT in BCR remain unknown.[28]
PSMA upstaging	PSMA PET has been shown to detect low-volume metastases that evade CI. The clinical implications of upstaging remain unclear. In a retrospective cohort study of 5,275 patients with high-risk or very high-risk PCa, the likelihood of PSMA upstage, as calculated using a novel PSMA nomogram, significantly predicted all long-term clinical end points, with 8-y concordance indices between 0.60 (OS) and 0.71 (PCSM).[39] The study authors concluded, "formerly occult, PSMA PET/CT-detectable nonlocalized disease may be the main driver of outcomes in high-risk patients."[39] Nomograms and other emerging tools may help refine patient selection for PSMA-PET, conserving resources and sparing lower-risk patients from unnecessary scans.[39,40]
Flare phenomenon	Changes in SUV_{max} in response to treatment could be interpreted as therapeutic failure, possibly causing discontinuation of therapy that is in fact working. It is unknown what the flare phenomenon—the appearance on initial PSMA scans of sclerotic (usually bone) lesions reflecting treated disease, not genuine progression—looks like in the context of advanced disease.
PSMA expression in benign tissue	PSMA is known to be expressed in benign tissues; as such, PSMA-based imaging can produce false-positive results, particularly in the ribs.[41] Interpreting results requires familiarity with such pitfalls.[27,36,42]
Interspecialty differences	Interspecialty differences in PSMA imaging strategies also require resolution. In clinical practice, committee members see a push toward or away from TPI depending on the expected initial treatment. A radiation oncologist may send a patient for PSMA imaging on the same day as the initial appointment, for example, while a urologist might perform CI first.

BCR, biochemical recurrence; CI, conventional imaging; FDG, fluorodeoxyglucose; OS, overall survival; PCa, prostate cancer; PCSM, prostate cancer–specific mortality; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy; RT, radiotherapy; SUV_{max}, maximum standardized uptake value; TPI, targeted precision imaging.

Earlier detection of metastatic PCa brings increased interest in MDTs intended to delay the need for systemic therapy.[11] In ORIOLE, PSMA PET-guided MDT increased 6-month progression-free survival compared with CI-guided MDT (95% vs 62%).[31] STOMP showed that choline PET-directed MDT improved median ADT-free survival compared with surveillance (21 months vs 13 months) and delayed endocrine resistance in men with BCR and 1 to 3 metastases.[32] In the POPSTAR pilot study, 48% of patients who underwent ^{18}F-NaF PET/CT-guided MDT achieved a 2 year free interval without any ADT.

Although RADAR VI presents consensus recommendations for initial and subsequent TPI imaging (Table 9), the optimal timing and frequency of serial imaging remain unknown.

Limitations of PSMA PET Imaging

PCa detection and localization with PSMA-based PET/CT remains an evolving technology. Table 10 explores the current limitations of PSMA and goals for ongoing research. Multiple novel PSMA-targeting radiotracers are under evaluation (Table 1), setting the stage for more widespread use of TPI.[33] Additional potential applications for TPI include tumor phenotyping (eg, PSMA-positive tumors) and the use of PSMA uptake intensity as a biomarker to predict response to PSMA-targeted therapy.[33] While TPI may ultimately prove useful for treatment monitoring, response criteria for both FDG and PSMA-PET are lacking at present.[34,35]

Recognizing the increasing role of PSMA PET in PCa management, the National Cancer Institute (NCI) Clinical Imaging Steering Committee PET PSMA Working Group recently developed guidance for integrating this imaging modality into clinical trials.[36] Falling short of reaching consensus, the group nonetheless outlined potential considerations, including the issue of stage migration—eg, from M0 to M1 CRCP based on PSMA PET findings—and its implications for trial eligibility, response assessment, and outcomes measures.

CONCLUSIONS

Advances in TPI are fundamentally changing PCa staging, patient selection, and management. Relative to CI, TPI demonstrates greater sensitivity and specificity in detecting residual or recurrent disease after initial treatment, often enabling individualized changes to subsequent treatment approaches. Moreover, TPI can detect metastases undetectable by CI, thereby identifying patients who may benefit from a new class of radioligand therapy (eg, ^{177}Lu-PSMA-617) for PSMA PET-positive mCRCP. Data showing improved clinical outcomes associated with TPI are accumulating. Until level I evidence catches up with technological advances, consensus guidance is critical to support health care professionals integrate TPI into their clinical decision-making. Findings from ongoing clinical trials will further refine the use of TPI in the routine management of patients with PCa.

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