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Synthesizing and Applying Molecular Targeted Imaging Results in Patients With Prostate Cancer (RADAR VII)

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Purpose: Molecular targeted imaging (MTI) is one of the most powerful new tools in the prostate cancer arsenal, but incorporation of MTI results into treatment decision making continues to be a challenge. Guidance is available for clinicians to determine when and how frequently MTI should be used, but clinicians also need to know how MTI results should influence management decisions.

Materials and methods: In this review, the Radiographic Assessments for Detection of Advanced Recurrence (RADAR) VII group has developed consensus guidance for the use of MTI in clinical decision making. RADAR VII sought to include all physicians involved in the management of prostate cancer, including urologists, medical oncologists, radiation oncologists, and nuclear medicine specialists.

Results: Recommendations were developed for the management of localized, biochemically recurrent, or nonmetastatic castrate-resistant prostate cancer (nmCRPC) by conventional imaging and metastatic disease by MTI. Recommendations were also developed for the treatment of patients with equivocal MTI results. These recommendations are based largely on clinical experience and limited clinical data because of a lack of high-quality, prospective studies regarding the role of MTI in clinical decision making. As such, the RADAR VII group also provides a framework for the incorporation of MTI into ongoing and future clinical trials to support the development of more robust recommendations.

Conclusions: We developed several recommendations for the interpretation and application of MTI results for patients with localized disease, biochemical recurrence, and nmCRPC on conventional imaging. These recommendations should be viewed within the context of the limited available evidence and the dynamic nature of prostate cancer research.

Key Words: prostatic neoplasms; positron emission tomography; prostatic neoplasms; castration-resistant

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THE Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group was originally convened in 2014 to develop consensus recommendations for the optimal timing of conventional imaging to

improve detection of metastatic prostate cancer.[1] Since that time, 5 additional RADAR groups have gathered to provide expert consensus on various topics related to the real-world management of prostate cancer that are not always addressed by published guidelines.[2-6] The first RADAR group to provide recommendations on the topic of molecular targeted imaging (MTI)—also referred to as targeted precision imaging or next-generation imaging—was RADAR III in 2019, at a time when MTI was still an investigational tool.[2] Since then, several advances have been made in the field of MTI, culminating in the recent approvals of several novel radiotracers for prostate cancer diagnosis and treatment. As a result, RADAR VI developed practical guidance regarding the timing and frequency of MTI for patients at various points in the prostate cancer journey.[6]

The availability of MTI represents an important step forward in the diagnosis and staging of localized and advanced prostate cancer. MTI can provide information about prostate cancer with high accuracy, sensitivity, and specificity relative to conventional imaging.[7] The ability for clinicians to distinguish between localized and metastatic disease is particularly critical, given the rapidly expanding landscape of systemic and metastasis-directed therapies for both metastatic hormone-sensitive prostate cancer (mHSPC) (also referred to as castrate-sensitive and castrate-naïve prostate cancer) and metastatic castrate-resistant prostate cancer (mCRPC).

Incorporation of MTI into everyday practice continues to be a challenge for several reasons, both clinical and operational. The RADAR VI group addressed several key clinical questions regarding MTI use, including when, how, and how frequently to perform MTI.[6] However, a key question remains: *How should MTI results influence management decisions?* Practical recommendations in this regard are limited, likely because of a lack of randomized controlled trials incorporating MTI at baseline. For example, the National Comprehensive Cancer Network (NCCN) does not distinguish their management recommendations based on the use of conventional imaging or MTI.[8] While currently available recommendations from the Advanced Prostate Cancer Consensus Conference provide some management guidance for unequivocal MTI results, equivocal results are common and present substantial difficulty for the treating physician.[9] Clinicians who manage prostate cancer would benefit from guidance for the incorporation of MTI results into clinical decision making, particularly for patients with newly diagnosed and biochemically recurrent disease.

MATERIALS AND METHODS

The RADAR VII group was convened in August 2022 to develop consensus pathways to address these questions and to provide practical guidance for clinicians who are faced with synthesizing and applying MTI results across a range of prostate cancer stages. The RADAR VII group sought to include all physicians directly involved in the management of prostate cancer and included urologists (n = 6), medical oncologists (n = 2), a radiation oncologist (n = 1), and a nuclear medicine specialist (n = 1). The 10 panel members were from 10 different US-based academic and community practices. The panel members were asked to review the literature on MTI and MTI-guided management before meeting in person. Literature reviews were conducted individually and nonsystematically.

The RADAR VII group met to discuss the application of MTI results to treatment decision making. The group followed a structure similar to that of the RADAR VI recommendations, evaluating the implications of MTI results by patient phenotype, considering stage migrations based on discordant conventional imaging/MTI results. For each disease stage, the panel evaluated the implications of equivocal, unifocal, oligometastatic, and disseminated disease on MTI. For the purposes of the RADAR VII recommendations, unifocal was defined as a single prostate cancer lesion identified by the interpreting radiologist; oligometastatic was defined as a limited number of prostate cancer lesions (maximum of 3-5) identified by the interpreting radiologist; and disseminated disease was defined as more than 3 to 5 prostate cancer lesions identified by the interpreting radiologist.[10] Throughout the discussion, the RADAR VII group referred to relevant prostate cancer guidelines related to conventional imaging and MTI, including those produced by the NCCN,[8] past RADAR groups,[1-6] the Advanced Prostate Cancer Consensus Conference,[9] and the National Clinical Trials Network (NCTN).[11] The use of MTI for establishing the diagnosis of prostate cancer was not discussed in this meeting.

RESULTS

General Principles of MTI for Treating Clinicians

Understanding MTI results remains a challenge for many treating clinicians. Standardized interpretation and reporting systems have been developed for prostate-specific membrane antigen (PSMA)-based positron emission tomography (PET)/CT (eg, PSMA-RADS, E-PSMA).[12-14] These reporting systems incorporate measures such as PSMA expression in lesions relative to levels in the blood pool, liver, and/or parotid gland.[13] Although PSMA-RADS and other interpretation methods have been associated with generally good inter-reader and intra-reader agreement,[15,16] the RADAR VII panel agreed that there has been limited uptake of standardized systems in routine MTI reporting. Therefore, inconsistent MTI results are common and may present treating clinicians with difficult decisions. When treating clinicians have questions about the information contained within an

MTI report, the panel agreed that reviewing MTI results with the interpreting physician can be an informative exercise. That said, as with any new imaging technology, there is an inherent learning curve for interpreting PSMA-based PET scans. Therefore, treating clinicians may also want to consider the experience level of the center as well as the interpreting physician and, when appropriate, consider seeking a second opinion through a center with experienced radiologists (eg, an academic or high-volume center with extensive experience in MTI interpretation).

Importantly, we would like to caution against overinterpretation of information contained within MTI reports beyond the conclusions of interpreting radiologists. In particular, it may be tempting for treating clinicians to use semiquantitative values such as the mean or maximum standardized uptake values (SUV_{mean} and SUV_{max}) to make treatment decisions. However, SUV_{mean} and SUV_{max} can be influenced by several factors beyond the subjective read, and there is currently no consistent, high-level evidence supporting this approach. Early data regarding the prognostic values of SUV_{mean} and SUV_{max} are conflicting. In one retrospective study of 848 men who underwent radical prostatectomy, higher SUV_{max} values were associated with worse biochemical recurrence–free survival and shorter time to biochemical recurrence.[17] However, in a separate retrospective study that specifically evaluated patients with indeterminate PSMA-based PET/CT results (n = 22), neither SUV_{max} nor the ratio of SUV_{max}:SUV_{mean} were associated with risk of progression.[18] Therefore, the RADAR VII panel recommends that SUVs should not be used to predict a patient's risk of progression or need for treatment. Instead, MTI results should be considered as binary (ie, positive or negative according to the interpreting physician) until more evidence is available supporting SUV thresholds. Similarly, MTI should not be used to monitor for treatment response until the clinical relevance of positive MTI results during treatment has been determined.

Equivocal or indeterminate MTI results remain one of the most challenging aspects of MTI integration into clinical practice. When MTI returns equivocal results, the RADAR VII group recommends a metastatic biopsy whenever possible, either by interventional approaches or by surgical approaches. However, the panel recognizes that biopsies may not always be feasible because of patient preference, technical challenges of bone biopsies, or small lesion size (eg, subcentimeter lymphadenopathy). In these cases, clinicians should consider obtaining additional imaging, including magnetic resonance imaging and/or CT. It is also reasonable to review the MTI results with the interpreting physician or to seek a second opinion, which may help provide additional insights. Once these approaches have been exhausted and the patient's risk of stage migration cannot be determined, the treating clinician still has a variety of established disease and patient factors that can contribute to treatment selection and sequencing. Key features that can be used in conjunction with MTI results to drive decision making include conventional imaging results, prostate-specific antigen (PSA) level and velocity, Gleason score, disease location and volume, patient performance status, life expectancy, and the overall risk of relapse or progression. Although these features become particularly relevant when a patient's MTI results are equivocal or indeterminate, they are globally relevant to all treatment decision making discussed herein.

Finally, it should be noted that several conditions have been associated with false-positive PSMA PET results.[19] For example, there is accumulating evidence in the literature suggesting that COVID-19 vaccination—and perhaps other vaccinations—may promote the uptake of radiotracers, including ^{68}Ga-PSMA-11, by axillary and supraclavicular lymph nodes.[20-22] Positive lymph nodes after COVID-19 vaccination are more common in patients who have received multiple doses, those with a short period between vaccination and MTI (<30 days), and those with a higher PSA level.[20] Other conditions associated with PSMA uptake include bone-related conditions (eg, osteomyelitis, fracture), inflammation and infection (eg, sarcoidosis, diverticulosis), benign neoplasms (eg, meningioma), and non-prostatic malignancies (eg, breast cancer).[19] Therefore, providers should be cognizant of the possibility of false positives and consider the metastatic patterns of prostate cancer when evaluating PSMA PET results. For example, in a patient with extensive PSMA lymph node uptake throughout the body, clinicians may consider obtaining vaccination history to evaluate for vaccine-related lymph node uptake.

MTI Stage Migration

MTI can be deployed across the prostate cancer spectrum for staging, with distinct implications according to disease state. Treatment decision making in prostate cancer requires clinicians to carefully weigh the risks and benefits of treatment alongside patient values and preferences. The benefits and risks of treatment—and patient goals for survival and quality of life—vary considerably based on whether patients are presenting with newly diagnosed or recurrent nonmetastatic disease on conventional imaging. Therefore, the RADAR VII group developed separate recommendations for each phenotype.

Newly Diagnosed Localized/Locally Advanced Prostate Cancer by Conventional Imaging. According to recommendations from the NCCN and RADAR VI, PSMA-based MTI can be used as both initial and confirmatory testing in patients with newly diagnosed prostate cancer.[6,8] As previously discussed, equivocal results for patients with localized and locally advanced prostate cancer on conventional imaging remain challenging. Local, definitive treatment of a patient with undetected metastatic disease by conventional imaging may put the patient at risk of unnecessary complications and could delay initiation of beneficial metastasis-directed therapy. By contrast, treatment of advanced disease with extended or even lifelong systemic therapy can have substantial quality-of-life effects on patients and may present more risks than benefits in a patient with localized disease by conventional imaging and indeterminate results by MTI, which may or may not represent true metastatic disease.[23] Nonetheless, given the greater diagnostic accuracy of MTI relative to conventional imaging, equivocal results should not be dismissed without consideration.[7] At this time, the RADAR VII recommendations for the integration of MTI into clinical decision making for localized disease on conventional imaging are based on clinical experience and limited clinical evidence.

As shown in Figure 1, biopsy is recommended in patients with localized disease and equivocal MTI results. When a biopsy has been obtained with sufficient tissue for interpretation, patients should be treated according to the biopsy results. However, in cases when a biopsy is not feasible or tissue samples are insufficient, we recommend adjuvant testing as outlined in the prior section. Treating clinicians should use the information gathered from these evaluations in conjunction with other disease characteristics for decision making.

Because the benefit-risk analysis between localized and advanced prostate cancer treatments differs so substantially, we recommend following the same recommended process for unifocal MTI results as for equivocal results. Treating clinicians should endeavor to confirm the presence of metastatic disease before initiating systemic treatment, including through additional imaging, discussion with the interpreting physician, and obtaining a second opinion. If, at the end of this process, positive MTI results remain the only evidence of metastatic disease, clinicians should review the option of treatment of metastatic disease, in addition to other interventions, during the shared decision-making discussion with the patient.

For oligometastatic and disseminated disease by MTI, biopsy can be considered, particularly if MTI results are discordant with the patient-risk level. That said, treating these cases as metastatic is a reasonable option in the absence of biopsy confirmation. Several treatment options are available for newly diagnosed mHSPC, including androgen receptor pathway inhibitors (ARPis) and chemotherapy.[24-28] Early evidence of metastatic disease by MTI may also present an opportunity to consider novel treatment combinations (ie, triplet therapy) with ARPis, chemotherapy, and androgen deprivation therapy based on the results of the ODM-201 in Addition to Standard ADT and Docetaxel in Metastatic Castration Sensitive Prostate Cancer (ARASENS) and PEACE-1 trials.[29,30] It should be noted that, at this time, all level 1 evidence for the

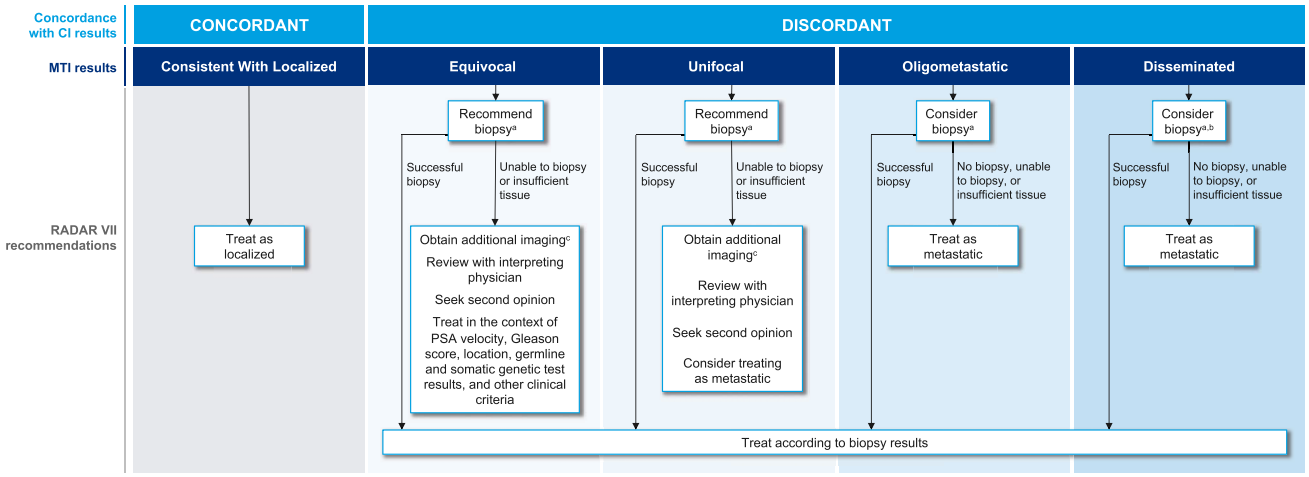

Figure 1. RADAR VII algorithm guiding treatment decision making based on MTI in patients with localized disease by CI. [a]Biopsy options include interventional radiology or lymph node dissection. [b]Consider for disease with high-risk features such as neuroendocrine differentiation, high-volume metastatic disease, and rapid PSA velocity, among others. [c]Consider magnetic resonance imaging and/or computed tomography. CI, conventional imaging; MTI, molecular targeted imaging; PSA, prostate-specific antigen.

treatment of metastatic prostate cancer comes from studies that enrolled patients based on conventional imaging. Nonetheless, extensive phase 3 trial data support the long-term survival benefit of systemic therapy in patients with mHSPC, even with substantial trial crossover and use of subsequent therapies. As such, the RADAR VII panel has adopted an "earlier is better" philosophy in our recommendation for managing advanced prostate cancer detected by MTI.[24-27]

Biochemical Recurrence by Conventional Imaging. The most extensive evidence for the use of MTI is in the biochemical recurrence (BCR) setting. RADAR VI recommends that MTI be considered in patients with rising PSA more than 0.2 ng/dL who may benefit from metastasis-directed therapy, regardless of whether patients meet the Phoenix criteria.[6,31]

As shown in Figure 2, RADAR VII recommendations for equivocal MTI results are similar for BCR and localized disease. Clinicians should determine whether adjuvant testing can provide clarity regarding the disease biology before determining treatment based on other disease factors, including PSA velocity, Gleason score, and location of disease. In contrast to our recommendations for localized disease, however, we endorse treating unifocal MTI results as metastatic disease if results cannot be confirmed by biopsy.

Our recommendations for unifocal and oligometastatic MTI results are based on evidence supporting the benefits of metastasis-directed therapy in patients with biochemical recurrence and lesions identified by MTI. In the phase 2/3 EMPIRE-1 trial, patients with detectable PSA after radical prostatectomy were assigned to receive radiation therapy (RT) directed by conventional imaging alone or RT directed by ^{18}F-fluciclovine PET/CT plus conventional imaging. After a median follow-up of more than 3.5 years, RT guided by MTI was associated with significantly extended BCR-free and persistence-free survival.[32] In the oligometastatic setting, the Surveillance or Metastasis-directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) and ORIOLE trials provide evidence that metastasis-directed therapy in patients with metastases detected by conventional imaging can extend progression-free survival and delay the need for systemic therapy.[33-35] Additional research will be needed to confirm that the results of STOMP and ORIOLE are applicable to populations with oligometastatic disease detected by MTI only. Until these studies are performed, data from STOMP and ORIOLE suggest that the benefits of metastasis-directed therapy in patients with BCR and MTI-detected unifocal or oligometastatic disease may outweigh the risks.

Nonmetastatic Castrate-Resistant Prostate Cancer by Conventional Imaging. It is likely that most patients with high-risk nonmetastatic castrate-resistant prostate cancer (nmCRPC) in fact have metastatic disease, albeit at previously undetectable levels.[6,36] As such, the RADAR VI group considered nmCRPC to be the most challenging disease state to provide recommendations for because of the uncertainty of the relevance of MTI results. Nonetheless, RADAR

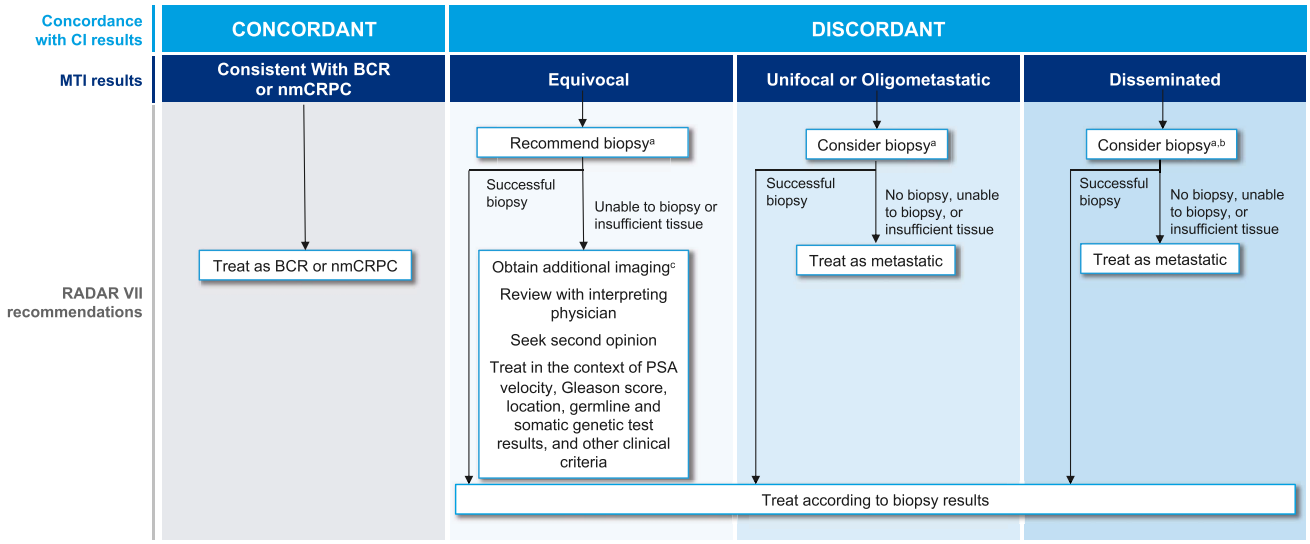

Figure 2. RADAR VII algorithm guiding treatment decision making based on MTI in patients with BCR or nmCRPC by conventional imaging. [a]Biopsy options include interventional radiology or lymph node dissection. [b]Consider for disease with high-risk features such as neuroendocrine differentiation, high-volume metastatic disease, and rapid PSA velocity, among others. [c]Consider magnetic resonance imaging and/or computed tomography. BCR, biochemical recurrence; CI, conventional imaging; MTI, molecular targeted imaging; nmCRPC, nonmetastatic castrate-resistant prostate cancer; PSA, prostate-specific antigen.

VI recommended MTI for patients with BCR and PSA progression on androgen deprivation therapy as long as metastasis-directed therapy could be considered.[6] Although the conceptual challenges of MTI and its relevance to disease biology remain, we found that for the purposes of MTI-based treatment decision making, nmCRPC was among the most straightforward of the disease states discussed. This is because many of the treatments approved for use in nmCRPC are also approved for mCRPC and, as such, integrating MTI results may not substantially change treatment decision making. This is particularly true in the first-line setting, where ARPis are preferred treatments in both disease states based on the results of the Androgen Receptor Antagonizing Agent for Metastasis-free Survival (ARAMIS), PROSPER, and Selective Prostate Androgen Receptor Targeting with ARN-509 (SPARTAN) trials in nmCRPC and the COU-AA-302 and PREVAIL trials in mCRPC.[8,37-41]

As shown in Figure 2, patients with unifocal, oligometastatic, or disseminated disease on MTI may be treated as mCRPC, which adds several options to the treatment landscape in addition to ARPis (ie, chemotherapy, immunotherapy, radioligand therapy). Patients with equivocal results should be treated within the context of the disease features and patient factors previously discussed. Given the overlapping biologic nature of nmCRPC and mCRPC, it is reasonable to treat those patients who are eligible (ie, those with PSA >2 ng/mL and PSA doubling time $\leq$10 months) with ARPis, which have been shown to extend survival in the context of nonmetastatic disease as determined by conventional imaging.[42-44]

The RADAR VII group's recommendations are supported by evidence that most patients with nmCRPC who meet the criteria of ARAMIS, PROSPER, and SPARTAN have metastatic disease by MTI. In a retrospective study of 200 patients with nmCRPC by conventional imaging and high-risk features (PSA doubling time $\leq$10 months or Gleason score of $\geq$8), 98% of patients had positive PSMA PET, including 55% with extrapelvic disease. When these data were used to stratify SPARTAN patients in a post hoc analysis, apalutamide conferred benefit in all patient subgroups, including those that were predictive of distant metastatic disease by PSMA PET.[36]

MTI and Clinical Trials

The RADAR VII panel emphasizes the need for more high-quality, prospective data regarding the clinical relevance of MTI results, which will require the incorporation of MTI in clinical trials. Challenges associated with including MTI in clinical trials include increased cost, lack of availability, and uncertainty regarding the effect of stage migration and/or response assessment on clinical trial enrollment and outcomes. Although the RADAR VII group recognizes these challenges, we, nonetheless, endorse endeavors to integrate MTI into ongoing and new clinical trials as an investigational biomarker. The NCTN Cooperative Groups identified barriers and developed guidance for the process of incorporating PSMA PET into clinical trials.[11] Although the NCTN guidance is specific to PSMA PET, the approaches discussed can likely be broadly applied to most novel radiotracer imaging methods.

RADAR VII endorses the NCTN recommendation of discouraging the use of PSMA PET to monitor treatment response and disease progression in clinical trials until the long-term outcomes with this approach have been better characterized. Furthermore, it is likely that radiographic progression will occur at an earlier time point with PSMA PET than with conventional imaging. Given that the clinical implications of progression on MTI have not yet been identified, it is possible that patients could be taken off trials despite the potential for continued benefit from therapy. Therefore, the NCTN also noted that PSMA PET findings should be observed until progression is noted on conventional imaging.[11] The RADAR VII group extends an additional recommendation to consider the incorporation of PSMA PET as an investigational biomarker and blinding the treating physician to PSMA PET results to prevent early and nonevidence-based discontinuation of treatment. Of note, efforts are underway to develop frameworks for treatment response evaluation with PSMA-based MTI. For example, Response Evaluation Criteria In PSMA PET/CT 1.0 were developed in 2022 to monitor patient response to ^{177}Lu-PSMA and may serve as an early response biomarker for prognosis.[45]

For ongoing trials that currently are using conventional imaging as an outcome measure, RADAR VII encourages protocol amendments to perform MTI at baseline (for newly enrolled patients) and at key follow-up points. Although the optimal frequency of MTI was not determined, it is reasonable that MTI should minimally be performed at evidence of treatment failure or progression. The RADAR VII group recognizes that there are cost and access issues inherent to these protocol amendments but, nonetheless, emphasizes the need for the incorporation of MTI into clinical trials as quickly as possible to obtain data regarding the use of this technology. One such example of a protocol amendment to add MTI to an ongoing clinical trial can be found in the phase 3 PROTEUS trial, which is evaluating perioperative apalutamide in patients with high-risk prostate cancer. PSMA PET imaging was added at 3 months after adjuvant therapy, at

biochemical failure, and every 6 months thereafter until distant metastasis or death.[46]

For future clinical trials in prostate cancer, the RADAR VII group endorses routine collection of PSMA PET at baseline and at prespecified points throughout the trial, in accordance with NCTN guidance. One option is to perform MTI at the same time as conventional imaging. Importantly, the use of MTI should not replace conventional imaging for primary end point analyses nor enrollment criteria until the implications of MTI have been fully characterized. Incorporating MTI into clinical trials and evaluating the concordance of MTI with conventional imaging findings and with patient outcomes will be critical to better understand the role of MTI in the future.

CONCLUSIONS

We have developed several recommendations for the synthesis and application of MTI results for patients with localized disease, BCR, and nmCRPC on conventional imaging. As with all RADAR consensus meetings, the RADAR VII group used the best available evidence at the time of development to draft best-practice recommendations. We recognize that best practices for prostate cancer management based on MTI results are expected to evolve, particularly as MTI is incorporated into clinical trials, as we have recommended here. Therefore, the RADAR VII recommendations should be viewed within the dynamic context of the evolving clinical landscape for prostate cancer.

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