Current Status of MRI and PET in the NCCN Guidelines for Prostate Cancer

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ABSTRACT

Prostate cancer (PCa) represents a significant source of morbidity and mortality for men in the United States, with approximately 1 in 9 being diagnosed with PCa in their lifetime. The role of imaging in the evaluation of men with PCa has evolved and currently plays a central role in diagnosis, treatment planning, and evaluation of recurrence. Appropriate use of multiparametric MRI (mpMRI) and MRI-guided transrectal ultrasound (MR-TRUS) biopsy increases the detection of clinically significant PCa while decreasing the detection of clinically insignificant PCa. This process may help patients with clinically insignificant PCa avoid the adverse effects of unnecessary therapy. In the setting of a known PCa, patients with low-grade disease can be observed using active surveillance, which often includes a combination of prostate-specific antigen (PSA) testing, serial mpMRI, and, if indicated, follow-up systematic and targeted TRUS-guided tissue sampling. mpMRI can provide important information in the post-treatment setting, but PET/CT is creating a paradigm shift in imaging standards for patients with locally recurrent and metastatic PCa. This article examines the strengths and limitations of mpMRI for initial PCa diagnosis, active surveillance, recurrent disease evaluation, and image-guided biopsies, and the use of PET/CT imaging in men with recurrent PCa. The goal of this review is to provide a rational basis for current NCCN Clinical Practice Guidelines in Oncology for PCa as they pertain to the use of these advanced imaging modalities.

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Role of Multiparametric MRI in Diagnosis

Conventional screening for prostate cancer (PCa) consists of digital rectal examination (DRE) and serum prostate-specific antigen (PSA) testing, followed by transrectal ultrasound (TRUS)–guided prostate biopsy. The role of multiparametric MRI (mpMRI) has become increasingly important as reflected by NCCN, American Urological Association (AUA), and European Association of Urology (EAU) recommendations (Table 1).[1–6] Specifically, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Prostate Cancer Early Detection recommend that mpMRI may be considered in men with indications for biopsy (eg, elevated PSA) to reduce the number of men undergoing biopsy that will in turn reduce the detection of indolent disease (and thus the risks of overdetection and treatment).[2,6] However, the guidelines point out that a negative mpMRI does not exclude the possibility of cancer, and that biomarkers and/or PSA density should be considered when deciding whether to avoid a biopsy in a man with a negative mpMRI result. mpMRI has additional roles in prostate cancer diagnosis. First, mpMRI can be integrated with TRUS imaging (MR-TRUS fusion) which as an increased detection rate of high-grade lesions.[8–12] Recently published mpMRI-based prediction models reduced unnecessary biopsies while being able to detect clinically significant disease.[13] Second, mpMRI has a role in the initial staging of intermediate-risk and high-risk patients by detecting extraprostatic extension (EPE), seminal vesicle invasion, and lymph node involvement. mpMRI also is helpful for selecting men who are suitable for nerve-sparing radical prostatectomy.[14] Third, mpMRI may facilitate exclusion of anterior cancer if PSA level increases and systematic TRUS biopsy results remain negative.[15]

Role of mpMRI in Active Surveillance

Active surveillance involves the active monitoring of men with seemingly indolent PCa with the goal of initiating therapy if tumor progression occurs.[2] Carefully selected patients for active surveillance have a very low risk of cancer-related death over a 10- to 15-year period while maintaining quality of life.[16] Higher grade, nonindolent PCa must be detected at diagnosis to identify men who require

Table 1. NCCN Guidelines for Prostate Cancer: Recommendations for the Use of Imaging[2]

Risk Group	Bone Scintigraphy	Abdominal/Pelvic Imaging	C-11 choline, 18-F fluciclovine, 18-F NaF PET/CT or PET/MRI
Very low risk and low risk	Not indicated	Consider mpMRI to confirm candidacy for active surveillance. During active surveillance, repeat mpMRI no more often than every 12 mo unless clinically indicated	Not indicated
Favorable intermediate risk	Not recommended for staging	Consider mpMRI to confirm candidacy for active surveillance. During active surveillance, repeat mpMRI no more often than every 12 mo unless clinically indicated Pelvic ± abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Not indicated
Unfavorable intermediate risk	Recommended if T2 and PSA >10 ng/mL	Pelvic ± abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Can be considered for equivocal results on initial bone scan
High risk	Recommended	Pelvic ± abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Can be considered for equivocal results on initial bone scan
Very high risk	Recommended	Pelvic ± abdominal imaging recommended if nomogram predicts >10% probability of pelvic lymph node involvement	Can be considered for equivocal results on initial bone scan
Regional recurrence AnyT,N1,M0	Recommended for symptoms and as often as every 6–12 mo while on ADT and for workup of progression	Abdominal/pelvic MRI or CT ± contrast is recommended for workup of progression	Consider for further soft tissue or bone evaluation during workup for progression
Metastatic (castration-naïve and -resistant) AnyT,anyN,M1	Recommended for symptoms and as often as every 6–12 mo during ADT in the castration-naïve setting: "…may be obtained regularly during systemic therapy to assess clinical benefit" For CRPC, "8–12 wk imaging intervals appear reasonable"	Abdominal/pelvic MRI or CT ± contrast is recommended for workup of progression: "…may be obtained regularly during systemic therapy to assess clinical benefit."	Consider for further soft tissue or bone evaluation during workup for progression in the castration-naïve setting

Abbreviations: ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; mpMRI, multiparametric MRI; NaF, sodium flouoride; PSA, prostate-specific antigen.

definitive treatment. Although guidelines differ regarding which patients are ideal for active surveillance, multiple studies concur that Gleason score should be ≤6 and mpMRI is without evidence of EPE, although some men with low-volume Gleason grade 3+4 disease (Grade Group 2) aged <70 years are considered for active surveillance.[17]

mpMRI has a clear role in the evaluation of patients before placement on active surveillance. mpMRI is becoming increasingly common in the active surveillance group to avoid overtreatment of low-risk PCa and avoid associated unnecessary morbidity.[14,17,18] The high negative predictive value of mpMRI, ranging as high as 90% to 100%, is relevant in determining clinically significant disease for establishing active surveillance eligibility.[19–21] Furthermore, mpMRI has poor sensitivity for low-volume Gleason 3+3 disease (Grade Group 1), which further exploits negative mpMRI results as a predictor of appropriateness for active surveillance.[22]

Consensus for inclusion into active surveillance depends on the Gleason score on MR-TRUS or conventional TRUS biopsy. The PICTURE trial showed that mpMRI had a sensitivity of 80.6% and specificity of 68.5% for a radiologic Likert score >4 (ie, high likelihood for cancer). This trial concluded that mpMRI could be used to avoid a repeat biopsy.[23] The PROMIS trial compared the diagnostic accuracy of MR-TRUS and conventional TRUS versus transperineal template mapping biopsies, and reported that MR-TRUS was more sensitive than TRUS (93% vs 48%) but less specific than TRUS (41% vs 96%). In addition, MR-TRUS detected up to 18% more men with clinically significant cancer.[24] Conversely, the PRECISION trial showed that targeted biopsy alone with up to 4 cores per lesion (and no systematic biopsy) was noninferior to systematic biopsy alone.[25] Despite this discrepancy, interpretation of these studies and others supports the perspective that although mpMRI enhances the

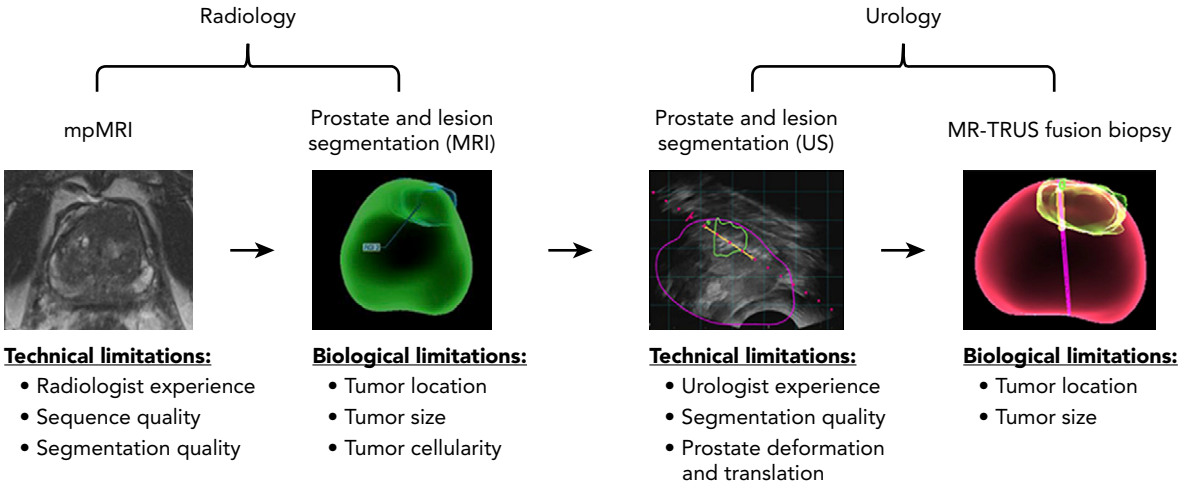

Figure 1. Limitations of mpMRI and MR-TRUS fusion. Shown are the individual components of the MRI workflow necessary to diagnose prostate cancer with MR-TRUS. Several technical and biologic limiations are listed that are potential weaknesses and can compound error in the detection and localization of clinically significant prostate cancer.
Abbreviations: mpMRI, multiparametric MRI; MR-TRUS, MRI-guided transrectal ultrasound; US, ultrasound.

detection of clinically significant cancer and decreases the detection of clinically insignificant cancer, both MR-TRUS and systematic TRUS should be used in tandem in the assessment of clinically significant disease.

The role of mpMRI in monitoring men on active surveillance is less defined. Currently, the percentage of patients on active surveillance upgrading to active treatment ranges from 14% to 41%.[26] Assessing the utility of mpMRI in upgrading these patients using clinically relevant end points of overall survival and disease-free survival is challenging, because the estimated 20-year prostate-specific mortality of patients on active surveillance is 2% to 3%, with some studies not yet reaching this follow-up duration.[27,28] Thus, there is an overall lack of consensus in defining disease progression.[29] The PRECISE study attempted to develop a series of recommendations for reporting mpMRI findings in men on active surveillance but lacked data to support these recommendations. Key recommendations from the PRECISE study include reporting index lesion size and conspicuity, EPE, or presence of metastases,[30] suggesting that mpMRI can effectively act as a safety net for patients on active surveillance through its ability to detect the onset of aggressive disease. Further data and analysis are essential before widespread adoption of these recommendations occurs.

Limitations of mpMRI and MR-TRUS Fusion Biopsy

mpMRI is an important tool in the initial evaluation of men with PCa, both for lesion detection and sampling using MR-TRUS biopsy. Multiple steps occur during the workup of a patient in whom there is concern for a clinically significant PCa, from the acquisition of the images to the MR-TRUS biopsy of the lesion, which involve both the radiologist and the urologist. These steps can be influenced by technical and biologic factors that have the potential to introduce significant errors into the workflow (Figure 1).

In the radiologic component of the biopsy workflow, several factors can reduce image quality and lesion conspicuity, including postbiopsy hemorrhage, rectal gas, hip prosthesis, or patient motion.[1,31] The PI-RADS (Prostate Imaging Reporting and Data System) guidelines issue a collection of minimum patient preparation and technical specifications necessary for a diagnostic study.[32] However, it must be noted that despite these specifications, there continues to be variability in image quality among centers.[33] The location of the lesion can influence detection as well. Not only are cancers within the transition zone less conspicuous due to the large amount of signal heterogeneity associated with benign prostatic hyperplasia, but apical peripheral zone lesions are missed more frequently.[34–36] In addition, smaller and less cellular lesions are less likely to be detected with mpMRI.[35] Next, radiologist interpretation may also pose a limitation in the use of mpMRI. One study of 409 men whose mpMRI studies were read by 9 radiologists identified marked variability in the PI-RADS distribution and yield from MR-TRUS biopsy. A wide range of 13% to 60% of men with a radiographically evident lesion scored equivocal or benign (PI-RADS version 2 score ≤3) harbored clinically significant cancer.[37] Prostate and lesion volume segmentation can pose a limitation. Prostate and tumor volumes are consistently underrepresented with mpMRI.[38,39] Placement of a TRUS device can cause significant gland deformation that increases the error in lesion sampling,

especially for smaller lesions. This phenomenon is becoming increasingly important, because many 3T mpMRI studies are performed and segmented without an endorectal device for MR-TRUS fusion.[39,40]

MR-TRUS fusion biopsies have limitations involving the urologists who perform the biopsy; as with radiologists, there is variability in experience, and interindividual variability in the segmentation of prostate volumes from ultrasound that are ultimately coregistered with the MRI dataset.[41,42] The technique may have inherent limitations. A recent study highlighted that clinically significant lesions in the dorsolateral and apical prostate were missed more commonly with MR-TRUS fusion, and conventional TRUS more commonly missed clinically significant lesions in the anterior prostate.[43] Together, these data are supported by studies that confirm mpMRI-guided biopsies may miss index lesions 5% to 20% of the time.[36,44–46] The biopsy approach may be important, because MR-guided transperineal biopsy has a significantly increased detection rate of clinically significant cancer compared with transrectal biopsy, which was primarily attributed to better anterior prostate sampling.[47] Therefore, these limitations must be factored into studies that use MR-TRUS biopsy specimens as a sole means to confirm the presence of malignancy.

These limitations introduce a potential problem in the clinical management of men with elevated PSA levels and negative mpMRI results who have not yet undergone prostate biopsy. Multiple retrospective studies have shown that clinically significant disease can be present despite negative mpMRI findings. Moreover, evaluation of mpMRI depends on multiple factors, including radiologist experience, lesion size, and lesion location.[36,48–51] Although more prospective evidence is needed, these data support the use of TRUS biopsy in this patient population. For these reasons, the NCCN Guidelines for PCa recommend a general "prostate biopsy" for initial clinical assessment that is not specific to conventional TRUS or MR-TRUS.[2] The NCCN Guidelines for PCa Early Detection state that mpMRI "can be considered before TRUS biopsy to inform biopsy decisions and to help identify regions of the prostate that may harbor cancer."[6]

In summary, use of mpMRI in PCa has a role in early detection; it can identify clinically significant cancer and the presence of extraprostatic disease. During active surveillance, it can be implemented with serial PSA levels and TRUS in the evaluation for disease progression, but its role is not as well defined. Although there are many advantages of mpMRI, limitations of diagnostic workflows need to be considered. Additional prospective clinical trials are needed to further define the role of mpMRI in improving patient outcomes, including its role in detecting and monitoring recurrent PCa.

Limitations of Imaging Strategies in Detecting Recurrent PCa

Imaging-based detection of recurrent PCa after definitive therapy with either radical prostatectomy or radiation therapy may not be as straightforward as the strategies used at initial diagnosis. The distinction between local recurrence, distant metastatic disease, and a combination of both is critical, because this will affect whether the patient will receive local salvage and or systemic treatment.[52] Therefore, imaging modalities that have the ability to detect recurrent local and distant metastatic disease to nodes, viscera, and the skeleton are relevant.

mpMRI has shown utility in the detection of local recurrence after radical prostatectomy, with specific emphasis on the dynamic contrast enhancement component of the examination. Sensitivities range from 71% to 100% and specificities range from 74% to 100%, but both depend on the size of the lesion and the PSA level.[53,54] Delaying local treatment until the site of recurrence is identified may be problematic in some cases, because many of these studies have shown increased rates of lesion detectability with median PSA levels $>$0.5 ng/mL, a threshold used for salvage therapy and associated with improved outcomes.[55]

MRI has the ability to detect osseous metastases with better sensitivity than bone scintigraphy,[56] but whole-body MRI techniques to detect metastatic disease are still under development.[57] MRI and CT assess nodal involvement indirectly through the use of morphology and diameter, which makes detection especially challenging for micrometastatic disease. These modalities are similar in their ability to detect involvement with sensitivity $<$40%.[58,59] Therefore, other modalities, specifically PET, have the potential to identify recurrent and metastatic disease with higher sensitivity and specificity.

Clinically Available PET Imaging Agents for Recurrent PCa

At least 60 active and recruiting clinical trials involve imaging of men with PCa. Furthermore, at least 30 radiopharmaceuticals that target various aspects of PCa biology have been or are being used in clinical trials (ClinicalTrials.gov).[60]

Only 4 of these PET tracers are addressed in the current NCCN Guidelines and cleared by the FDA for use in patients with PCa: 18-F fluorodeoxyglucose (FDG), 18-F sodium fluoride (NaF), 18-F fluciclovine, and C-11 choline.[2] There may be a role for 18-F FDG in the setting of biochemical recurrence. In one study, FDG identified the site of local recurrence in only 8.1% of cases.[61] However, FDG may be useful in quantification of disease burden in patients with poorly differentiated cancer and

who have developed neuroendocrine PCa.[62] The Centers for Medicare & Medicaid Services covers 18-F FDG-PET only for subsequent treatment strategy guidance (ie, initial treatment strategy indications are not reimbursed).[63] The current NCCN Guidelines state that "FDG-PET should not be used routinely: in men with PCa, particularly not in initial staging.[2] Therefore, other PET tracers may be considered (Table 1).

NaF is a bone-targeting agent that is useful only for evaluating osseous metastases; it is FDA-approved to define areas of osteoblastic activity, independent of cancer type. Compared with conventional bone scintigraphy using [^{99m}Tc] MDP, NaF-PET/CT has better image quality and resolution that can enhance lesion conspicuity.[64] A meta-analysis identified a pooled sensitivity and specificity for NaF of 96.2% and 98.5%, respectively, compared with 57% and 98% for bone scintigraphy.[65] One drawback to NaF-PET/CT is enhanced detection of benign processes, such as arthritis, which can make interpretation of these scans more problematic than scintigraphy. The current NCCN Guidelines recommend that bone scintigraphy be performed first and that other imaging modalities, including 18-F NaF-PET/CT or PET/MRI be considered for subsequent evaluation of equivocal findings.[2] Furthermore, earlier detection of osseous metastases "may result in earlier use of newer and more expensive therapies, which may not improve oncologic outcome or overall survival."[2] This perspective may evolve in light of more recently published findings in the STOMP trial that show that early treatment of oligometastatic (including osseous) sites identified by choline PET/CT led to improved androgen deprivation therapy–free survival.[66] Other PET agents that are able to identify sites of osseous, nodal, and visceral metastases may diminish the need for an imaging study that is used solely to identify osseous metastases.[67]

C-11 choline is a PET tracer that targets cell membrane lipid biosynthesis that is enhanced in cancer cells. C-11 choline is FDA-approved for identifying sites of disease in patients with biochemical recurrence. Current NCCN Guidelines state that C-11 choline PET/CT or PET/MRI can be considered in the workup of men with recurrent PCa.[2] It can be considered after bone scintigraphy for evaluation of equivocal findings.[2] The sensitivity of C-11 choline positively correlates with serum PSA level and dose of the agent administered.[68] After radical prostatectomy, a European single-center study of 4,426 patients identified that PSA level of 1.16 ng/mL was the optimal cutoff to detect recurrent disease with C-11 choline PET/CT; 26% patients had detectable disease with PSA level <1 ng/mL and an additional 44% of patients had detectable disease with PSA level 1 to 2 ng/mL.[69] Additional US studies have proposed similar PSA cutoffs of 1.4 to 2.0 ng/mL.[70,71] Optimal PSA cutoffs for C-11 choline PET/CT in men who have received radiation therapy are less clear due to lack of data and the presence of PSA from viable prostate gland. In a study of 161 patients with PSA increasing after primary RT who underwent C-11 choline PET/CT, 87% were found to have sites of recurrence, 59% of which were histologically confirmed.[72] The median PSA level of the cohort was 7.8 ng/mL, but with PSA levels less than the Phoenix criteria threshold median of 1.9 ng/mL,[73] 71% had confirmed sites of recurrence.

18-F fluciclovine is an amino acid analog whose uptake is enhanced in cancer cells. 18-F fluciclovine is FDA-approved for identifying sites of disease in men with biochemical recurrence. Current NCCN Guidelines state that 18-F fluciclovine PET/CT or PET/MRI can be considered in the workup of men with recurrent PCa and after bone scintigraphy for evaluation of equivocal findings.[2] The detection rates of 18-F fluciclovine positively correlate with serum PSA measurements. In a study of 100 patients, 18-F fluciclovine detected disease in 21% of men with PSA level <1 ng/mL, 29% of men with PSA level 1 to 2 ng/mL, 45% of men with PSA level 2 to 3 ng/mL, and 59% of men with PSA level >3 ng/mL. The true positive rates of 18-F fluciclovine in this trial were higher than that of C-11 choline.[74] Another study of 83 men with biochemical recurrence identified an optimal PSA cutoff of 1.41 ng/mL, similar to the proposed optimal PSA thresholds for choline.[75] It remains unclear whether the differences between these 2 tracers are clinically meaningful.

An important finding regarding the performance of 18-F fluciclovine PET/CT in the detection of recurrent PCa may be that its sensitivity depends on the location of disease recurrence. A recent study of 93 men with biochemical recurrence identified specificities of 40% and 97% for prostatic bed and extraprostatic bed foci, respectively.[76] An additional study of 53 men had similar findings, with specificities of 56% and 100%, respectiely.[77] A similar study of 596 patients showed 88.1% sensitivity and 32.6% specificity for detecting recurrent disease in the prostate bed.[78] 18-F fluciclovine imaging may be equivalent to or better than bone scintigraphy in the evaluation of osseous metastatic disease. In one study, 18-F fluciclovine PET/CT identified positive foci in 7 of 66 patients who had negative findings on bone scintigraphy and CT, although evidence of histologic validation in this cohort was not obtained.[79] As with C-11 choline, more prospective studies are necessary to assess a role for these individual PET/CT imaging methods in the evaluation of men with biochemical recurrence.

Prostate-specific membrane antigen (PSMA) is a transmembrane antigen that is upregulated in PCa. Many PET tracers have been and are being developed to target this

protein but none are FDA-approved.[60,80,81] Current evidence suggests that PSMA tracers have the potential to outperform currently FDA-approved PET tracers at low serum PSA levels, but are not currently part of the NCCN Guidelines.[2,82,83]

Conclusions

Clinically available PET tracers may have the ability to affect clinical workflows for men with PCa, especially those with biochemical recurrence. However, caution must be used when interpreting results of the studies discussed, because many fail to include histologic validation of the tracer on a lesion-by-lesion basis. In addition, no substantial prospective evidence exists to show that earlier PET detection of nodal metastatic disease improves outcomes in patients. The realization that individual PET tracers detect different sites of disease in a given individual is not surprising, because these PET tracers target independent biologic processes and the differences in tracer uptake can result from clonal heterogeneity between metastases, prior chemotherapy, and androgen deprivation therapy. Future studies might use more than one PET tracer to localize and quantify disease burden as a means to overcome the heterogeneity of PCa biology not only among individuals but also among lesions in the same patient.

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