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THE ROLE OF IMAGING IN SCREENING SPECIAL FEATURE: REVIEW ARTICLE

The emerging role of imaging in prostate cancer secondary screening: multiparametric magnetic resonance imaging and the incipient incorporation of molecular imaging

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ABSTRACT

An increasingly robust body of evidence indicates that multiparametric MRI (mpMRI) prior to prostate biopsy can improve the detection of clinically significant prostate cancer while avoiding unnecessary biopsies. As a result, the use of mpMRI and biopsy platforms that allow for the real-time fusion of mpMRI and transrectal ultrasound images is now routinely used in clinical practice. On the horizon, molecular imaging offers the promise of improved sensitivity relative to mpMRI and early data would suggest that the combination of mpMRI and positron emission tomography using radiotracers targeting prostate-specific membrane antigen provide a more accurate assessment than either modality alone. In this review, we examine the current role of imaging to aid in the initial diagnosis of prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is the second most common malignancy among males worldwide.¹ PCa, when found early, is potentially curable^{2,3} and historically screening with physical examination [*i.e.* digital rectal exam (DRE)] and serum prostate specific antigen (PSA) levels have been used to facilitate early diagnosis. When a concerning abnormality is appreciated on DRE or a patient is found to have an elevated PSA level, a biopsy is generally performed in order to histologically confirm the presence of cancer.⁴

Non-targeted sextant biopsies were once the standard of care to diagnose PCa, although 12-core biopsies that include apical and far-lateral sampling are now routinely employed as this approach has been found to significantly improve the detection of clinically significant cancer.⁵ Prostate biopsy is typically carried out with real-time transrectal ultrasound (TRUS) guidance to allow adequate visualization of the boundaries of the prostate. In many cases, patients will not have undergone other imaging at the time of biopsy and PCa lesions are often occult on TRUS.

Indeed, even 12-core biopsies can miss clinically significant PCa given the relatively small volume of the prostate that is physically sampled with each core.⁶

Many patients with an elevated PSA will be overdiagnosed with non-clinically significant cancer. Recent work has shown overdiagnosis from non-targeted biopsies ranges between 23 and 42%, with an overdiagnosed prostate cancer being defined as disease for which the patient is diagnosed and treated but that would not be clinically apparent during the patient's life.⁷ Furthermore, although biopsy can allow for the definitive diagnosis of the presence of PCa, it is not without risks, and patients may experience pain, bleeding, and infection.⁸

Management options for clinically-localized PCa include active surveillance, watchful waiting, radical prostatectomy, external beam radiation therapy, brachytherapy, and ablation.^{2,3} The appropriate treatment will be determined based on the patient's age, medical comorbidities, PSA, tumor grade, local extent of disease,⁹ and a reasoned discussion

with the patient to allow for collaborative and informed decision-making. Of particular relevance to this review, it should be noted that patients who are believed to harbor very low risk disease (defined by the National Comprehensive Cancer Network as clinical T1c, Gleason score ≤ 6 , PSA < 10 ng ml⁻¹, fewer than three positive cores on biopsy with each core being $\leq 50\%$ cancer, and PSA density < 0.15 ng/ml/g)¹⁰ should preferentially be managed with active surveillance in order to minimize unnecessary morbidity associated with aggressive treatment modalities;^{2,3} thus it is of paramount importance to accurately determine a given patient's Gleason score. Decision-making and outcomes vary considerably among patients with intermediate- and high-risk disease including surgical approach (e.g. necessity of pelvic lymph node dissection) and aggressiveness of recommended therapy (e.g. concurrent use of androgen deprivation therapy with external beam radiation therapy).^{2,3} It is in this context that imaging has come to play an evolving role in PCa secondary screening (i.e. risk stratification beyond primary screening with PSA and DRE) and diagnosis. In this review, we will examine the current role of imaging, primarily multiparametric MRI (mpMRI), in evaluating patients with suspected PCa prior to definitive diagnosis.

Role of mpMRI and mpMRI/TRUS Fusion-Guided Biopsy
mpMRI allows for detailed anatomic evaluation of the prostate and surrounding structures within the pelvis. This includes delineation of intraprostatic lesions, identification of extraprostatic extension, and potentially even recognition of N1 or M1 disease outside of the prostate such as in locoregional lymph nodes or in the bony structures of the pelvic girdle (although early nodal and osseous metastases may be inconspicuous at the time of initial mpMRI evaluation).¹¹ Lesions in the prostate can be assessed for their malignant potential based on their intrinsic imaging characteristics and correlations between mpMRI findings and histopathology have demonstrated that the imaging modality is an accurate predictor of the presence of PCa.¹²⁻¹⁴

Complete mpMRI includes a series of key pulse sequences, including T_2 weighted images that are used to assess the anatomic size of a lesion as well as the relationship of the lesion to important landmarks such as the prostate capsule and the seminal vesicles,¹⁵ diffusion-weighted images (DWI) that provide information on the cellular density/potential aggressiveness of a site of PCa by examining the degree of diffusion restriction of water molecules in tissue,¹⁶ and a T_1 weighted dynamic contrast-enhanced (DCE) acquisition that generates a read-out of the vascularity of a PCa lesion. Generally, the less T_2 signal, the more diffusion restriction, and the more vascularity these lesions exhibit, the more likely it is that a clinically significant cancer will be found histologically. MR spectroscopy may also be supplementarily used to evaluate the ratio of metabolites choline and citrate in a given voxel within the prostate as prostate cancers have increased choline and decreased citrate levels. As the ratio of choline to citrate increases, the potential aggressiveness for a detected prostate cancer also increases.^{17,18}

The combination of these imaging features has been standardized using the Prostate Imaging Reporting and Data System

(PI-RADS) lexicon, and lesions can be risk stratified based on their PI-RADS scores, with higher scores indicating a greater likelihood of the presence of high grade PCa.^{19,20} Although the original version of PI-RADS was published in 2012,¹⁷ it was the updated version released in 2015 (PI-RADS Version 2)²⁰ that dramatically popularized this standardized reporting system. Many of the key studies that have demonstrated the utility of mpMRI in identifying lesions that should undergo biopsy actually predate the widespread adoption of PI-RADS, although future studies will almost certainly make use of this system.

The method used to accomplish image guidance and fusion should also be considered. No matter how accurate an imaging modality is at identifying a site of PCa, the information from that modality must be able to be effectively used during real-time biopsy guidance in order to positively impact the biopsy yield. In-bore real-time MRI-guided biopsy is expensive and time-consuming and is therefore, little used in modern practice. Knowing the location of a lesion on mpMRI allows the provider performing the biopsy to cognitively target the TRUS biopsy and obtain core samples from the same approximate location in the prostate. However, a number of systems are available that provide a means of mapping data from imaging such as mpMRI onto the real-time TRUS images providing true mpMRI-TRUS fusion.²¹ This real-time methodology appears to be a more effective approach than cognitive targeting.²² In general, it has been suggested that real-time fusion allows for improved targeting of small lesions and may decrease the expertise necessary to perform targeted biopsies relative to cognitive methods.²³ Deformation of the prostate between the mpMRI and TRUS as well as incorporation of non-MRI imaging data is possible with at least one commercial system.^{24,25}

A number of studies have demonstrated the superiority of using image-guidance as opposed to a non-targeted templated approach for prostate biopsy. For example, Siddiqui et al compared mpMRI/TRUS fusion biopsy to 12-core systematic TRUS biopsy in 582 males and observed a higher rate of high grade cancer detection with the image-guided approach.²⁶ More specifically, the authors noted that of the 315 males in whom PCa was confirmed, 81 (32%) had Gleason score upgrading as a result of targeted biopsy. Additionally, 67% more tumors with Gleason $\geq 4 + 3$ were found with use of mpMRI/TRUS fusion. Corroborative findings of high rates of detection of clinically significant PCa by mpMRI-guided biopsy with or without potential decreased rates of detection of clinically insignificant disease have also been reported other groups including Kasivisvanathan et al²⁷ and Sonn et al.²⁸

In a particularly important prospective study of 1003 patients who underwent both targeted and blind biopsy, mpMRI/TRUS fusion targeted biopsy identified 30% more high-risk cancers and 17% fewer low-risk cancers than 12-core systematic biopsy alone.²⁹ The combination of targeted and non-targeted biopsies found additional 103 cancers (22% of the total diagnosed), of which 83% were low-risk, 12% were intermediate-risk, and 5% were high-risk.²⁹ Although many of the cancers identified by including non-targeted biopsy were low-risk, the finding

Figure 1. Representative examples of mpMRI of prostate cancer. (A–D) PI-RADS 3 lesion. (A) Axial T2-weighted image demonstrates subtle asymmetric decreased T2 signal in the posteromedial peripheral zone (PZpm) of the left base (white arrow). (B) This corresponds to isointense signal on DWI and (C) mildly hypointense signal observed on the ADC map (white arrow). (D) This area does not exhibit early enhancement on DCE. Overall, this lesion was deemed to be PI-RADS 3. On targeted biopsy, this area yielded a small focus of atypical glands from the targeted biopsy and a small of focus of prostatic adenocarcinoma (Gleason score $3 + 3 = 6$) involving less than 5% of one core. (E–H) PI-RADS 4 lesion. (E) Axial T2-weighted image shows homogenous moderately hypointense T2 focus (white arrow) measuring less than 1.5 cm in maximum dimension in the anterior peripheral zone (PZa) of the left apex. (F) At the same location, there is focal hyperintense signal on DWI (white arrow) and (G) hypointense signal on the ADC map (white arrow). (H) Furthermore, this area exhibits early enhancement on DCE (white arrow). This lesion was concluded to be PI-RADS 4, and on targeted biopsy this area yielded clinically significant prostatic adenocarcinoma (Gleason score $3 + 5 = 8$) involving two of two cores. (I–L) PI-RADS-5 lesion. (I) Sagittal T2-weighted image demonstrates a homogenous moderately hypointense T2 mass (white arrow) measuring greater than 1.5 cm in maximum dimension in the posterior lateral zone (PZpl) of the left mid and base of the prostate with extension into the left seminal vesicle. (J) This lesion can also be clearly seen on an axial T2-weighted image where there is blurring of the capsule adjacent to the left neurovascular bundle which may represent extra-prostatic extension (white arrow), (K) with corresponding hypointense signal on the ADC map (white arrow). (L) This mass also exhibited equivocal early enhancement on DCE (white arrow). This mass was reported as PI-RADS 5. On targeted biopsy, multiple areas of prostatic adenocarcinoma were found with the highest Gleason score ($4 + 5 = 9$) involving two of two cores from the left base. ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced; DWI, diffusion-weighted imaging; PZa, anterior peripheral zone; PZpl, posterolateral zone; PZpm, posteromedial peripheral zone.

that some males harboring high-risk PCa were identified only on the non-targeted biopsy cores would argue that a combined approach is necessary.

The most compelling data to date on the use of mpMRI as part of PCa secondary screening is from the Diagnostic Accuracy of Multi Parametric MRI and TRUS Biopsy in Prostate

Cancer (PROMIS) trial³⁰ and the Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not? (PRECISION) trial.³¹ PROMIS was designed and implemented before the publication of PI-RADS and, as such, makes use of a 5-point Likert scale that may be relatively equivalent to PI-RADS³² and categorized patients as highly unlikely (1) unlikely (2) equivocal (3) likely (4) and highly likely (5) to have

Table 1. Selected radiotracers for PCa imaging and their potential roles in the secondary screening population

Radiotracer	Mechanism of action	Potential for use in PCa secondary screening
¹¹ C-choline	Component of cell membrane synthesis and cell signaling	Likely minimal due to non-specific uptake in benign hypermetabolic processes such as BPH
¹⁸ F-fluciclovine	Uptake by amino acid transporters ASC and LAT1	Likely minimal due to non-specific uptake in benign hypermetabolic processes such as BPH
¹⁸ F-DCFBC	Binds to PSMA	Likely minimal due to low sensitivity and suboptimal tumor-to-background ratios
^{99m} Tc-trofolostat	Binds to PSMA	Moderate: a SPECT radiotracer that may have particular utility in parts of the world that lack a large installed base of PET scanners
¹⁸ F-DCFPyL	Binds to PSMA	High due to apparent excellent sensitivity and specificity
⁶⁸ Ga-PSMA-HBED-CC	Binds to PSMA	High due to apparent excellent sensitivity and specificity

PCa, Prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; SPECT, single photon emission computed tomography;

clinically significant PCa.³⁰ Clinically significant PCa was defined as Gleason score $\geq 4 + 3$ or at least 6 mm of a core being involved by cancer. Under the PROMIS protocol, 576 males without previous prostate biopsy underwent mpMRI (on a 1.5-Tesla magnet) followed by a TRUS-guided saturation/mapping biopsy as well as a standard 10 to 12 core biopsy. Using the mapping biopsy as the reference standard, the diagnostic performance of mpMRI was then compared to standard template biopsy for ability to detect clinically-significant prostate cancer. The use of mpMRI as a means to select males for biopsy would have led to 27% of patients avoiding a biopsy with 5% fewer clinically insignificant cancers. Additionally, mpMRI allowed for the detection of 18% more clinically significant cancers detected. Thus, based on data from the PROMIS study, the dual problems of prostate biopsy (*i.e.* overdiagnosis of clinically insignificant cancers and missed clinically significant cancers) are both partially addressed by the incorporation of mpMRI into the work-up of males being screened for PCa.

Recent work by the PRECISION study group further supports the findings in the PROMIS trial.³¹ Their study was a multi-center, randomized, non-inferiority trial which randomized 500 patients who had not had prior prostate biopsy. Those patients who underwent pre-biopsy evaluation with mpMRI on either 1.5- or 3.0-Tesla scanners had increased detection of clinically significant cancers (38 vs 26%) and fewer diagnoses of clinically insignificant cancers as compared to the standard TRUS-guided 10 to 12 core biopsies.³¹ Findings on mpMRI in the PRECISION trial were categorized according to PI-RADS v. 2.³¹ Important considerations in future studies include the continued incorporation of PI-RADS for improved homogeneity across centers and the potential for overall better imaging given the increase in the installed base of 3.0-Tesla MRI scanners.

Contemporary implementation of prostate mpMRI
At Johns Hopkins, patients are scanned on a 3.0-Tesla scanner with a body coil using large and small fields-of-view of the pelvis. Endorectal coils are no longer used in our prostate imaging protocol, as in 3.0-Tesla systems such coils have not correlated with significant diagnostic benefit compared to the use of only body coils.^{33,34} Endorectal coils can, however, improve the

detection of certain features of PCa when used with 1.5-Tesla systems, including the determination of T3a (extraprostatic extension) and T3b (seminal vesicle invasion) disease.^{34–36} Prior to scanning, patients are injected intramuscularly with 1 mg glucagon in order to reduce bowel motility. Axial T_2 turbo spin echo fat-saturated images of the pelvis and high-resolution axial, sagittal, and coronal T_2 , coronal T_2 3D SPACE, axial DWI with apparent diffusion coefficient (ADC) images, pre- and post-contrast T_1 , and axial MASK/PROSTREAM images of the prostate are acquired. Patients receive 0.1 mmol/kg intravenous gadolinium at 3 ccs⁻¹ for the DCE images. Although not in routine use at our Johns Hopkins, MR spectroscopy may also be obtained by sampling volumes of interest (VOIs) throughout the prostate based on the axial T_2 images to measure metabolite levels of choline and citrate to detect the presence of prostate cancer and predict its aggressiveness.

Acquired images are evaluated by a radiologist specialized in reading prostate mpMRI, and any lesions found are characterized based on their size, location, intrinsic signal characteristics and enhancement patterns. This characterization is then translated into a PI-RADS score.²⁰ Patients with PI-RADS 3 and above lesions have VOIs segmented in separate analysis software and the VOIs are then exported for use during mpMRI/TRUS fusion biopsy (Figure 1).

The evolving role of molecular imaging

Although mpMRI has emerged as a means by which to increase the sensitivity and specificity for the detection of clinically significant PCa in patients requiring biopsy, it is nonetheless imperfect and will fail to show approximately 20% of clinically significant prostate tumors.³⁷ This limitation of prostate mpMRI has been a contributing factor in the drive to develop molecular imaging agents to reliably localize sites of PCa (Table 1). The most common molecular imaging agent in the field of oncology is the glucose analog 2-deoxy-2-[¹⁸F]fluoro-D-glucose (¹⁸F-FDG), which homes to hypermetabolic/glycolytically active tumors and is labeled with the positron emitting radionuclide ¹⁸F for imaging with positron emission tomography (PET). However, ¹⁸F-FDG lacks any role in PCa secondary screening due to its variable uptake in the disease. Other metabolism-based PET

Figure 2. Images from a Koelis UroStation platform for carrying out targeted fusion biopsies of the prostate. (A) Axial image from a ^{11}C -choline PET/CT with foci of increased uptake targeted for biopsy (orange and red circles). As discussed in the text, other PCa radiotracers (such as those targeted against PSMA) are likely to be more advantageous for guiding biopsies, but systems such as the Koelis UroStation are agnostic to the radiotracer that is used. (B-C) Representative images of both targeted (cylinders within spheres) and non-targeted (cylinders without spheres) biopsy cores from a patient undergoing biopsy for suspected PCa. The use of deformation algorithms that more accurately portray the locations of targets within the prostate after the endorectal insertion of the ultrasound probe and biopsy device as well as advanced methods of tracking the sites of biopsy back to the original diagnostic cross-sectional imaging are likely to find increased use in the future. PCa, prostate cancer; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

radiotracers including ^{11}C -choline³⁸ and ^{18}F -fluciclovine³⁹ also exist. ^{11}C -choline PET takes advantage of the increased metabolic demand in PCa for choline, which is used both in cell membrane formation and cellular signaling.⁴⁰ ^{18}F -fluciclovine PET uses the increased activity of the ASCT2 and LAT1 amino acid transporters in PCa.⁴¹ However, ^{11}C -choline³⁸ and ^{18}F -fluciclovine³⁹ have generally also not borne out as appropriate

Figure 3. Images from a 78-year-old male presenting with an elevated PSA of 8.7 ng ml⁻¹. (A) Axial T_2 weighted image demonstrating focal, low T_2 signal in the PZpm measuring 1.2 cm in largest dimension (white arrow). (B) Axial ADC map also demonstrates low signal at this location (white arrow). Based on these findings, this lesion was assigned a PI-RADS score of 4. (C) Axial ^{18}F -DCFPyL PET and (D) axial ^{18}F -DCFPyL PET/CT images show that there is abnormal, very intense radiotracer uptake corresponding to the site of the PI-RADS 4 lesion [black arrow in (C) and white arrow in (D)]. Targeted TRUS biopsy using volumes drawn on both the mpMRI and PET images yielded Gleason 5 + 4 = 9 high-risk PCa. ADC, apparent diffusion coefficient; PSA, prostate specific antigen; PZpm, posteromedial peripheral zone; TRUS, transrectal ultrasound.

for detecting PCa confined to the prostate due to non-specific uptake that prevents reliable differentiation of PCa from areas of inflammation or benign prostatic hyperplasia.

The most promising data on molecular imaging of prostate cancer have been obtained using radiotracers developed to bind to cancer-specific molecular targets. One of the more promising targets is prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein that is nearly universally expressed in PCa with expression levels positively correlating to disease aggressiveness.^{42,43} In a small study of 13 patients imaged, utilizing an early generation small molecule targeting PSMA (^{18}F -DCFBC), the specificity of PET for the detection of highly aggressive PCa (sum Gleason score 8 and 9 lesions greater than 1.0 ml in size) appeared to be higher than MRI, although it should be noted that full mpMRI was not performed as no DCE sequence was obtained.⁴⁴

More promising data has recently emerged with higher-affinity PMSA-targeted compounds that suggest the future role that these radiotracers can play in PCa secondary screening. More specifically, the single photon emission tomography (SPECT) radiotracer $^{99\text{m}}\text{Tc}$ -trofolastat was found to have uptake in 98/105 (94%) of patients with NCCN intermediate- and high-risk PCa.⁴⁵ Additionally, the uptake of this radiotracer was found

to directly correlate with Gleason score. Similarly, in a recent study including 25 males with biopsy-proven NCCN high-risk PCa (T3a disease, sum Gleason score ≥ 8 , or PSA >20 ng ml⁻¹), Gorin, et al reported that abnormal focal radiotracer uptake of the second-generation PSMA-targeted agent ¹⁸F-DCFPyL was visible in all 25 patients.⁴⁶ Even more compelling, however, are data from a study by Eiber and colleagues that found the PSMA-targeted PET radiotracer ⁶⁸Ga-PSMA-HBED-CC [also referred to in the literature as ⁶⁸Ga-PSMA and ⁶⁸Ga-PSMA-11] to be more sensitive than mpMRI for the detection of PCa in a cohort of 53 imaged males (49/53 (92%) vs 35/53 (66%)).⁴⁷ The combination of the two modalities produced the highest sensitivity, with cancer visible in 52/53 (98%) patients.⁴⁷ The superiority of PET/MRI in this context carried over into an AUC analysis [AUC of PET/MRI 0.88 vs 0.83 for PET alone ($p = 0.002$) and 0.73 ($p < 0.001$) for mpMRI]. Taken together, the aforementioned data strongly suggest that PSMA-targeted radiotracers should be investigated as a tool to improve the yield of prostate biopsy in the secondary screening population.

Discussion mpMRI-guided prostate biopsy has unequivocally been shown to increase the yield of high risk cancers when compared to non-targeted systematic biopsies.^{29,48} As such, in the post-PROMIS and post-PRECISION era, the question should be asked as to whether any male with an elevated PSA or abnormal DRE should undergo an unguided/blind biopsy. While cost and availability need to be considered when discussing the employment of mpMRI for such a common disease as PCa, the data are compelling that males with clinically significant PCa have a better chance of being appropriately diagnosed with mpMRI followed by biopsy. Further, males with an elevated PSA/abnormal DRE who would not benefit from biopsy can avoid unnecessary treatment for clinically insignificant disease and also avoid the morbidity of biopsy (which, as noted earlier, can

include pain, hemorrhage, and infection)⁸ by being worked-up with mpMRI. It is furthermore important to note that not all suspicious prostate MR findings when biopsied will yield malignancy. Prostatitis, areas of hemorrhage, and benign prostatic hypertrophy nodules can all be mistaken for malignancy without appropriate clinical context.^{9,49} To date, guidelines have not completely embraced the idea of imaging prior to biopsy in males suspected of harboring PCa. The NCCN has stated that “MRI is not recommended routinely prior to initial prostate biopsy”,⁵⁰ although as data continue to mount as to the benefits of secondary screening with imaging, these recommendations are likely to evolve.

The future of imaging in PCa secondary screening may hinge on the potential success of molecular imaging agents along with further improvements and availability of technology for successful biopsy guidance. Preliminary data has shown the possible additive value of PSMA-targeted PET radiotracers to mpMRI and this should be prospectively investigated in larger studies. As the installed base of PET/MRI scanners increases, such simultaneous multimodal imaging may evolve to be the means by which patients are imaged prior to undergoing biopsy for suspected PCa. Additionally, advancements in the ability to reliably correlate mpMRI and molecular imaging data with real-time TRUS images (Figures 2 and 3) have the potential to help maximize the diagnostic yield while minimizing morbidity from prostate biopsy.

CONFLICT OF INTEREST

AL is the co-founder and chief executive officer of Koelis, Inc, the manufacturer of the Urostation prostate biopsy platform. MGP has served as a consultant for Progenics Pharmaceuticals, the licensor of ¹⁸F-DCFPyL. MGP and SPR receive research funding from Progenics Pharmaceuticals.

REFERENCES

1. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends—an update. *Cancer Epidemiol Biomarkers Prev* 2016; **25**: 16–27. doi: <https://doi.org/10.1158/1055-9965.EPI-15-0578>
2. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. *J Urol* 2017; doi: <https://doi.org/10.1016/j.juro.2017.11.095>
3. Sanda MG, Cadeddu JA, Kirkby E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part II: recommended approaches and details of specific care options. *J Urol* 2018; **199**: 990–7. doi: <https://doi.org/10.1016/j.juro.2018.01.002>
4. Welch HG, Fisher ES, Gottlieb DJ, Barry MJ. Detection of prostate cancer via biopsy in the medicare-SEER population during the PSA era. *J Natl Cancer Inst* 2007; **99**: 1395–400. doi: <https://doi.org/10.1093/jnci/djm119>
5. Bjurlin MA, Taneja SS. Standards for prostate biopsy. *Curr Opin Urol* 2014; **24**: 155–61. doi: <https://doi.org/10.1097/MOU.0000000000000031>
6. Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay MD. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? *Can Urol Assoc J* 2013; **7**: 293–8. doi: <https://doi.org/10.5489/cuaj.1248>
7. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. *J Natl Cancer Inst* 2009; **101**: 374–83. doi: <https://doi.org/10.1093/jnci/djp001>
8. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, et al. Systematic review of complications of prostate biopsy. *Eur Urol* 2013; **64**: 876–92. doi: <https://doi.org/10.1016/j.eururo.2013.05.049>
9. Verma S, Rajesh A. A clinically relevant approach to imaging prostate cancer: review. *AJR Am J Roentgenol* 2011; **196**(3 Suppl): S1–S10. doi: <https://doi.org/10.2214/AJR.09.7196>
10. Network NCC. Prostate Cancer (Version 2.2017). 2017. Available from: https://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf [December 1, 2017].
11. Turkbey B, Brown AM, Sankineni S, Wood BJ, Pinto PA, Choyke PL. Multiparametric prostate magnetic resonance imaging in the evaluation of prostate cancer. *CA Cancer J*

- Clin* 2016; **66**: 326–36. doi: <https://doi.org/10.3322/caac.21333>
12. Portalez D, Mozer P, Cornud F, Renard-Penna R, Misrai V, Thoulouzan M, et al. Validation of the European Society of Urogenital Radiology scoring system for prostate cancer diagnosis on multiparametric magnetic resonance imaging in a cohort of repeat biopsy patients. *Eur Urol* 2012; **62**: 986–96. doi: <https://doi.org/10.1016/j.eururo.2012.06.044>
 13. Turkbey B, Mani H, Shah V, Rastinehad AR, Bernardo M, Pohida T, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. *J Urol* 2011; **186**: 1818–24. doi: <https://doi.org/10.1016/j.juro.2011.07.013>
 14. Renard-Penna R, Mozer P, Cornud F, Barry-Delongchamps N, Bruguère E, Portalez D, et al. Prostate imaging reporting and data system and likert scoring system: multiparametric MR imaging validation study to screen patients for initial biopsy. *Radiology* 2015; **275**: 458–68. doi: <https://doi.org/10.1148/radiol.14140184>
 15. Weinreb JC, Blume JD, Coakley FV, Wheeler TM, Cormack JB, Sotito CK, et al. Prostate cancer: sextant localization at MR imaging and MR spectroscopic imaging before prostatectomy—results of ACRIN prospective multi-institutional clinicopathologic study. *Radiology* 2009; **251**: 122–33. doi: <https://doi.org/10.1148/radiol.2511080409>
 16. Gibbs P, Tozer DJ, Liney GP, Turnbull LW. Comparison of quantitative T2 mapping and diffusion-weighted imaging in the normal and pathologic prostate. *Magn Reson Med* 2001; **46**: 1054–8. doi: <https://doi.org/10.1002/mrm.1298>
 17. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G. European society of urogenital R. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012; **22**: 746–57.
 18. Westphalen AC, Coakley FV, Qayyum A, Swanson M, Simko JP, Lu Y, et al. Peripheral zone prostate cancer: accuracy of different interpretative approaches with MR and MR spectroscopic imaging. *Radiology* 2008; **246**: 177–84. doi: <https://doi.org/10.1148/radiol.2453062042>
 19. Rosenkrantz AB, Oto A, Turkbey B, Westphalen AC. Prostate imaging reporting and data system (PI-RADS), version 2: a critical look. *AJR Am J Roentgenol* 2016; **206**: 1179–83. doi: <https://doi.org/10.2214/AJR.15.15765>
 20. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS prostate imaging - reporting and data system: 2015, version 2. *Eur Urol* 2016; **69**: 16–40. doi: <https://doi.org/10.1016/j.eururo.2015.08.052>
 21. Cornud F, Brolis L, Delongchamps NB, Portalez D, Malavaud B, Renard-Penna R, et al. TRUS-MRI image registration: a paradigm shift in the diagnosis of significant prostate cancer. *Abdom Imaging* 2013; **38**: 1447–63. doi: <https://doi.org/10.1007/s00261-013-0018-4>
 22. Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, et al. Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. *J Urol* 2013; **189**: 493–9. doi: <https://doi.org/10.1016/j.juro.2012.08.195>
 23. Wysock JS, Rosenkrantz AB, Huang WC, Stifelman MD, Lepor H, Deng FM, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. *Eur Urol* 2014; **66**: 343–51. doi: <https://doi.org/10.1016/j.eururo.2013.10.048>
 24. Moldovan P, Udrescu C, Ravier E, Souchon R, Rabilloud M, Bratan F, et al. Accuracy of elastic fusion of prostate magnetic resonance and transrectal ultrasound images under routine conditions: a prospective multi-operator study. *PLoS One* 2016; **11**: e0169120. doi: <https://doi.org/10.1371/journal.pone.0169120>
 25. Ukimura O, Desai MM, Palmer S, Valencirina S, Gross M, Abreu AL, et al. 3-Dimensional elastic registration system of prostate biopsy location by real-time 3-dimensional transrectal ultrasound guidance with magnetic resonance/transrectal ultrasound image fusion. *J Urol* 2012; **187**: 1080–6. doi: <https://doi.org/10.1016/j.juro.2011.10.124>
 26. Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. *Eur Urol* 2013; **64**: 713–9. doi: <https://doi.org/10.1016/j.eururo.2013.05.059>
 27. Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. *J Urol* 2013; **189**: 860–6. doi: <https://doi.org/10.1016/j.juro.2012.10.009>
 28. Sonn GA, Chang E, Natarajan S, Margolis DJ, Macairan M, Lieu P, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. *Eur Urol* 2014; **65**: 809–15. doi: <https://doi.org/10.1016/j.eururo.2013.03.025>
 29. Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015; **313**: 390–7. doi: <https://doi.org/10.1001/jama.2014.17942>
 30. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multiparametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017; **389**: 815–22. doi: [https://doi.org/10.1016/S0140-6736\(16\)32401-1](https://doi.org/10.1016/S0140-6736(16)32401-1)
 31. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018; **378**: 1767–77. doi: <https://doi.org/10.1056/NEJMoa1801993>
 32. Rosenkrantz AB, Kim S, Lim RP, Hindman N, Deng FM, Babb JS, et al. Prostate cancer localization using multiparametric MR imaging: comparison of prostate imaging reporting and data system (PI-RADS) and likert scales. *Radiology* 2013; **269**: 482–92. doi: <https://doi.org/10.1148/radiol.13122233>
 33. Gawlitza J, Reiss-Zimmermann M, Thörmer G, Schaudinn A, Linder N, Garnov N, et al. Impact of the use of an endorectal coil for 3 T prostate MRI on image quality and cancer detection rate. *Sci Rep* 2017; **7**: 40640. doi: <https://doi.org/10.1038/srep40640>
 34. Kim BS, Kim TH, Kwon TG, Yoo ES. Comparison of pelvic phased-array versus endorectal coil magnetic resonance imaging at 3 Tesla for local staging of prostate cancer. *Yonsei Med J* 2012; **53**: 550–6. doi: <https://doi.org/10.3349/ymj.2012.53.3.550>
 35. Engelbrecht MR, Jager GJ, Laheij RJ, Verbeek AL, van Lier HJ, Barentsz JO. Local staging of prostate cancer using magnetic resonance imaging: a meta-analysis. *Eur Radiol* 2002; **12**: 2294–302. doi: <https://doi.org/10.1007/s00330-002-1389-z>
 36. Hricak H, White S, Vigneron D, Kurhanewicz J, Kosco A, Levin D, et al. Carcinoma of the prostate gland: MR imaging with pelvic phased-array coils versus integrated endorectal-pelvic phased-array coils. *Radiology* 1994; **193**: 703–9. doi: <https://doi.org/10.1148/radiology.193.3.7972810>
 37. de Rooij M, Hamoen EH, Fütterer JJ, Barentsz JO, Rovers MM. Accuracy of

- multiparametric MRI for prostate cancer detection: a meta-analysis. *AJR Am J Roentgenol* 2014; **202**: 343–51. doi: <https://doi.org/10.2214/AJR.13.11046>
38. Souvatzoglou M, Weirich G, Schwarzenboeck S, Maurer T, Schuster T, Bundschuh RA, et al. The sensitivity of [11C]choline PET/CT to localize prostate cancer depends on the tumor configuration. *Clin Cancer Res* 2011; **17**: 3751–9. doi: <https://doi.org/10.1158/1078-0432.CCR-10-2093>
 39. Turkbey B, Mena E, Shih J, Pinto PA, Merino MJ, Lindenberg ML, et al. Localized prostate cancer detection with 18F FACBC PET/CT: comparison with MR imaging and histopathologic analysis. *Radiology* 2014; **270**: 849–56. doi: <https://doi.org/10.1148/radiol.13130240>
 40. Welle CL, Cullen EL, Peller PJ, Lowe VJ, Murphy RC, Johnson GB, et al. ¹¹C-choline PET/CT in recurrent prostate cancer and nonprostatic neoplastic processes. *Radiographics* 2016; **36**: 279–92. doi: <https://doi.org/10.1148/rg.2016150135>
 41. Nanni C, Schiavina R, Brunocilla E, Boschi S, Borghesi M, Zanoni L, et al. 18F-Fluciclovine PET/CT for the detection of prostate cancer relapse: a comparison to 11C-Choline PET/CT. *Clin Nucl Med* 2015; **40**: e386–91. doi: <https://doi.org/10.1097/RLU.0000000000000849>
 42. Ross JS, Sheehan CE, Fisher HA, Kaufman RP, Kaur P, Gray K, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. *Clin Cancer Res* 2003; **9**: 6357–62.
 43. Perner S, Hofer MD, Kim R, Shah RB, Li H, Möller P, et al. Prostate-specific membrane antigen expression as a predictor of prostate cancer progression. *Hum Pathol* 2007; **38**: 696–701. doi: <https://doi.org/10.1016/j.humpath.2006.11.012>
 44. Rowe SP, Gage KL, Faraj SF, Macura KJ, Cornish TC, Gonzalez-Roibon N, et al. ¹⁸F-DCFBC PET/CT for PSMA-based detection and characterization of primary prostate cancer. *J Nucl Med* 2015; **56**: 1003–10. doi: <https://doi.org/10.2967/jnumed.115.154336>
 45. Goffin KE, Joniau S, Tenke P, Slawin K, Klein EA, Stambler N, et al. Phase 2 study of ^{99m}Tc-trofolostat SPECT/CT to identify and localize prostate cancer in intermediate- and high-risk patients undergoing radical prostatectomy and extended pelvic LN dissection. *J Nucl Med* 2017; **58**: 1408–13. doi: <https://doi.org/10.2967/jnumed.116.187807>
 46. Gorin MA, Rowe SP, Patel HD, Vidal I, Mana-Ay M, Javadi MS, et al. Prostate specific membrane antigen targeted ¹⁸F-DCFpYl positron emission tomography/computerized tomography for the preoperative staging of high risk prostate cancer: results of a prospective, phase II, single center study. *J Urol* 2018; **199**: 126–132. doi: <https://doi.org/10.1016/j.juro.2017.07.070>
 47. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous ⁶⁸Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. *Eur Urol* 2016; **70**: 829–36. doi: <https://doi.org/10.1016/j.eururo.2015.12.053>
 48. Panebianco V, Barchetti F, Sciarra A, Ciardi A, Indino EL, Papalia R, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. *Urol Oncol* 2015; **33**: 17.e1–17.e7. doi: <https://doi.org/10.1016/j.urolonc.2014.09.013>
 49. Kitzing YX, Prando A, Varol C, Karczmars GS, Maclean F, Oto A. Benign conditions that mimic prostate carcinoma: MR imaging features with histopathologic correlation. *Radiographics* 2016; **36**: 162–75. doi: <https://doi.org/10.1148/rg.2016150030>
 50. Network NCC. NCCN flash updates: NCCN guidelines updated. 2017. Available from: <https://www.nccn.org/about/news/ebulletin/ebulletindetail.aspx?ebulletinid=735> [December 1, 2017].