Utility of Multiparametric Magnetic Resonance Imaging as a Predictor of Clinically Significant Prostate Cancer in a Sub-Saharan African Population

Mariah Kerubo Obino[1], *Edward Ng'ang'a Chege*[2], *Sudhir Vinayak*[2], *Samuel Gitau Nguku*[2]

[1]Department of Radiology and Imaging, Aga Khan University Hospital, Nairobi, Kenya

[2]Department of Radiology and Imaging, Aga Khan University, Nairobi, Kenya

Correspondence to: Dr. Mariah Kerubo Obino; email: mariahobino@gmail.com

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Summary

Background: Traditionally, the diagnosis of prostate cancer was based on increased prostate-specific antigen level or an abnormal digital rectal examination and confirmed histologically following biopsy. Consequently, a proportion of men without cancer or with clinically insignificant disease undergo unwarranted prostate biopsies and experience resultant complications. Pre-biopsy multiparametric magnetic resonance imaging (MP-MRI) is vital in determining those with clinically significant cancer who need biopsy and those with a negative MRI who can safely avoid unnecessary biopsy. **Methods:** The diagnostic accuracy of MP-MRI using transrectal ultrasound-guided biopsy as the reference test was established for 133 men who had undergone MRI and biopsy. The MRI images were reviewed and reported by two independent consultant radiologists. Clinically significant cancer was defined as Prostate Imaging Reporting and Data System score ≥3 on multiparametric MRI and Gleason score ≥3 + 4 (grade group ≥2) on histology. **Results:** MP-MRI of the prostate was found to have 92% sensitivity, 47.8% specificity, 86.8% negative predictive value (NPV) and 62% positive predictive value for the diagnosis of prostate cancer. **Conclusion:** MP-MRI has a high sensitivity and a high NPV, validating its use in pre-biopsy evaluation of men at risk of prostate cancer to safely avoid unnecessary prostate biopsy and to guide biopsy of suspicious lesions.

Keywords: MRI prostate, Prostate cancer, Clinically significant prostate cancer, Prostate Imaging Reporting and Data System (PI-RADS), Gleason score

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Introduction

Prostate cancer is one of the most commonly diagnosed cancers among men in Africa and second most common cancer in men worldwide, with lower survival rates among men of African descent (1–3). African men have been reported to disproportionately suffer from prostate cancer, with higher incidence, advanced stage of disease, and higher Gleason score at presentation than the rest of the world (4,5). This is attributed to genetic differences, particularly in sub-Saharan Africa, higher poverty levels, and lower levels of screening (4–9). Wallace et al. studied the tumor biology of prostate cancer and found significant differences in the tumor immunobiology between American men of African descent and those of European descent (10).

In the recent past, there has been a shift from the traditional approach of patients with an increased

prostate-specific antigen (PSA) and/or an abnormal digital rectal examination undergoing a prostate biopsy for histological confirmation to having a prostate magnetic resonance imaging (MRI) done in the first instance to determine which patient would benefit from the biopsy as well as to guide transrectal ultrasound (TRUS)-guided biopsy (11–13). Multiparametric MRI (MP-MRI) of the prostate is a useful adjunct to PSA particularly in screening. Although a PSA cutoff of 4 ng/mL has an excellent negative predictive value (NPV), it has been found to have a low positive predictive value (PPV) of 30% (14,15), since it is also usually increased in benign prostatic enlargement and prostatitis (16,17). There is no definite PSA cutoff to discriminate between clinically significant and insignificant prostate cancer(14). Consequently, men without cancer may undergo unnecessary biopsies, which are not only painful and uncomfortable but also have potential risks, including rectal bleeding, hematospermia, hematuria, infection, and the worst-case scenario is life-threatening sepsis, which occurs in 1-4% (12,18).

Non-targeted systematic core TRUS-guided biopsy may detect clinically insignificant cancer, but, more crucially, it may miss clinically significant cancer (11,12,16). This makes MP-MRI an important component in the diagnostic pathway, as it provides information on tissue anatomy, gland volume, cellularity, and contrast enhancement characteristics as well as size and location of lesions seen and evidence of extracapsular tumor extension (19,20). There is good evidence that prostate MRI detects higher-grade disease that is clinically significant and may overlook low-risk disease, which is likely to be indolent. Patients with clinically insignificant/low-risk/indolent disease undergo active surveillance, whereas those with high-risk/aggressive disease are treated with hormonal therapy, surgery, or radiotherapy depending on the stage (11). Consequently, MP-MRI performed pre-biopsy can preclude the need for biopsy if the prostate gland is normal or no suspicious lesion is seen (Prostate Imaging Reporting and Data System [PI-RADS] categories 1 and 2) (21). Meanwhile, PI-RADS category 4 and 5 lesions are suspicious and require histological confirmation of prostate cancer. Localization of the suspicious lesions by MRI followed by targeted TRUS-guided biopsy has led to better yield and detection of prostate cancer than systematic biopsy. Cognitive fusion, in particular, is helpful in resource-limited settings, as it does not require additional expertise beyond interpreting the MRI and conventional TRUS-guided biopsy technique for the ultrasound operator(22).

The aim of this study was to determine the diagnostic performance of MP-MRI in predicting clinically significant prostate cancer in a sub-Saharan population. Although studies on the value of prostate MP-MRI have been done elsewhere, data on MP-MRI on the African population are limited. This study on the value of prostate MRI in an African population is important particularly due to the differences in tumor biology, genetic differences, and seemingly more aggressive disease.

Materials and Methods

This was a cross-sectional study at a tertiary university hospital using retrospectively collected data. Ethical approval and waiver of patient consent were obtained from the institution's Research and Research Ethics Committees (Ref: 2018/REC-44(v2)).

The inclusion criteria were patients who had both MP-MRI of the prostate and histology done (systematic 10-12 core TRUS-guided biopsy or prostatectomy) between January 2016 and March 2019. Patients on treatment or those who were previously treated for prostate cancer prior to the above procedures were excluded.

Imaging technique

Prostate MP-MRI was performed using Philips Ingenia 3.0 T (Philips, Amsterdam, the Netherlands) or GE Signa Explorer 1.5 T (GE Healthcare, Chicago, IL, USA) using a body array coil with standardized sequences obtained in all patients based on the European Society of Urogenital Radiology (ESUR) recommendations. The following standard sequences were obtained: Anatomical sequences: T1- and T2-weighted axial (small and normal field of view), sagittal, and coronal views; functional sequences: Diffusion-

weighted imaging with low and high b values (b0, b800, and b1400) as well as T1-weighted dynamic contrast-enhanced sequences following administration of gadolinium-based contrast medium.

Workflow

1. Patients who met the inclusion criteria were identified, anonymized, and given reference numbers.
2. MRI images of these patients were provided to reader 1 (consultant radiologist with 3 years' experience in reporting MRI of the prostate) and reader 2 (consultant radiologist with 2 years' experience) who reported each of the studies independently and assigned a PI-RADS category ± other diagnosis, e.g., benign prostatic hyperplasia (BPH) and prostatitis.

PSA levels were provided to the readers.

3. Data obtained was analyzed alongside histology results as follows:

- A negative MP-MRI was defined as a PI-RADS score of 1 or 2.
- A positive MP-MRI was defined as a PI-RADS score of 3, 4, or 5.
- Clinically insignificant prostate cancer was defined as Gleason score 3+3 (grade group I).
- Clinically significant prostate cancer was defined as Gleason score ≥3+4 (grade groups II, III, IV, or V).

Disagreement between readers 1 and 2 in assigning PIRADS score was resolved by consensus.

- 2×2 contingency tables were constructed with true-positive, true-negative, false-negative, and false-positive results.
- Diagnostic accuracy (sensitivity, specificity, NPV, and PPV) was calculated.

Results

One hundred thirty-three patients met the inclusion criteria out of a total of 334 MP-MRIs done in our institution between January 2016-March 2019. Figure 1 shows the inclusion and exclusion characteristics of the study population. The mean age of the patients studied was 64.4 years (range, 43-80 years). Table 1 shows the demographic and gland volumes of 133 patients as well as the PSA and PSA density of 120 patients (no PSA results were available for 13 patients).

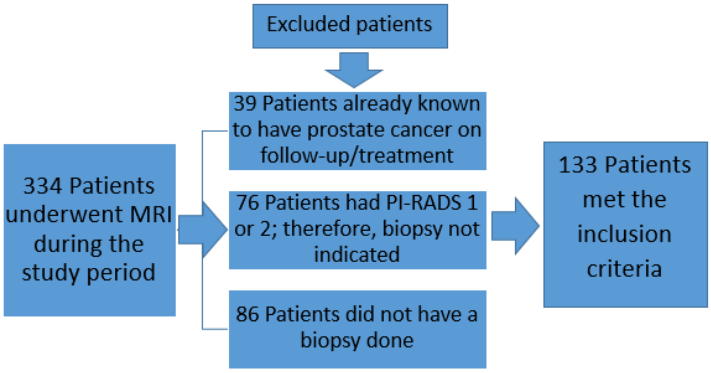

Figure 1. Inclusion and exclusion criteria for study population.

Table 2 shows the assigned PI-RADS categories. Prostate cancer was detected in 92 (69%) of the patients, with 64 (70%) of the patients with cancer having clinically significant disease (Gleason 7-10/grade groups II-V) and 28 (30%) patients having clinically insignificant cancer Gleason 3+3=6 (grade group I).

Table 1. Baseline characteristic and PSA density

CHARACTERISTIC	MEDIAN [RANGE]
Age (years)	64 [43-80]
Gland volume (mL)	44.5 [12.5-242]
PSA (ng/mL) (n=120)	14.9 [1.8-3605]
PSA density (n=120)	0.33 [0.053-46.2]

PSA, prostate-specific antigen.

Table 2. Overall assigned PI-RADS categories (n=133)

PI-RADS CATEGORY	FREQUENCY (PERCENTAGE)
2	38 (28.57)
3	8 (6.02)
4	23 (17.29)
5	64 (48.12)

PI-RADS, Prostate Imaging Reporting and Data System.

Forty-one (31%) patients had no cancer but had benign histological findings, including benign prostatic tissue, BPH, high-grade prostatic intraepithelial neoplasia, prostatitis, and atypical small acinar cell proliferation (Table 3). Table 4 shows the diagnostic accuracy results of MP-MRI.

Table 3. Histology results (n=133)

GLEASON SCORE	FREQUENCY (PERCENTAGE)
Benign/negative	41 (31)
6	28 (21)
7	28 (21)
8	19 (14)
9	15 (11)
10	2 (2)

The interobserver agreement of the two readers following dichotomization of the PI-RADS scores (1-2, negative; 3-5, positive) was 83.46%, which corresponds to a Cohen's kappa of 0.59 (moderate agreement using Landis and Koch scale).

Table 4. Diagnostic accuracy results of prostate multiparametric magnetic resonance imaging

	Diagnostic accuracy (%)	95% confidence interval
Sensitivity	92.19	(87.63-96.75%)
Specificity	47.83	(39.34-56.32%)
Positive predictive value	62.11	(53.86-70.35%)
Negative predictive value	86.84	(81.10-92.59%)
Prevalence	48.12	(39.63-56.61%)

The correlation between PSA density (calculated as PSA/prostate gland volume) and histology results was determined for 120 patients only (13 patients did not have a record of PSA levels) using Pearson's chi square test. The PSA density was dichotomized as <0.15 and >0.15. The relationship was statistically significant with $p<0.001$.

Discussion

MP-MRI had a high sensitivity of 92.19% (95% confidence interval [CI], 87.63-96.75%) in detecting clinically significant cancer, which supports its capability in predicting presence of prostate cancer in patients assigned PI-RADS 4 and 5 and validates the usefulness of pre-biopsy MP-MRI in the selection of patients who need biopsy. The high NPV of 86.84% (95% CI, 81.1-92.59%) signifies a high likelihood that clinically significant cancer is absent when MP-MRI is negative. This strongly implies that, in patients with PI-RADS 1 or 2 category, an unnecessary biopsy may be safely avoided while reducing overdiagnosis of low-grade disease. The patient in Figure 2 who had a negative biopsy followed by an MRI that did not reveal any suspicious findings, only BPH changes, would have safely avoided the unnecessary biopsy if the MRI was done prior.

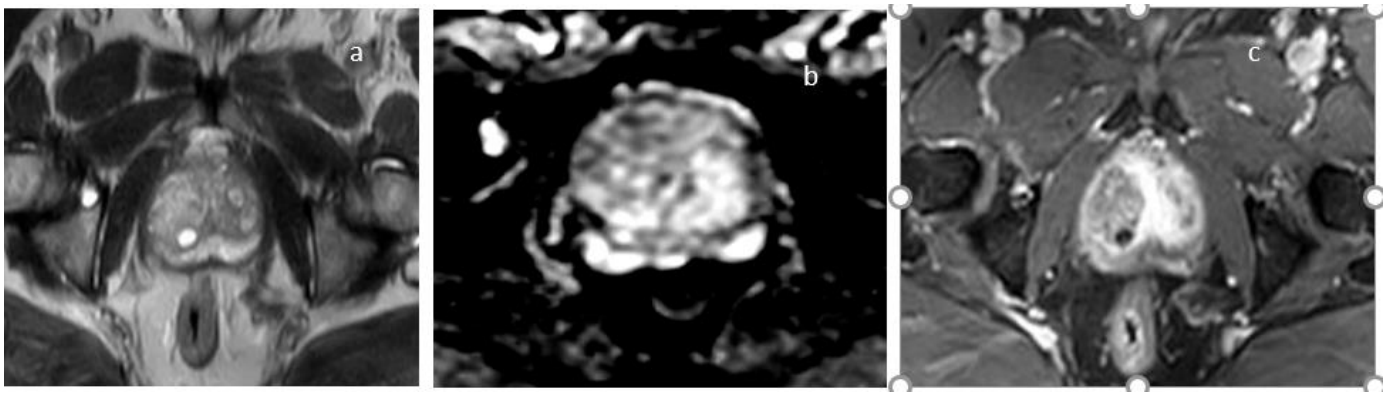

Figure 2. A 66-year-old man with increased prostate-specific antigen level of 11 ng/mL. The result of non-targeted biopsy was negative. Subsequent magnetic resonance imaging revealed an enlarged prostate gland with an approximate volume of 178 mL. However, no T2-hypointense lesion (a) was seen with corresponding low signal on apparent diffusion coefficient maps (b) or abnormal post-contrast enhancement (c). A small circumscribed lesion seen in the right transition zone (a) did not show restricted diffusion or abnormal enhancement in subsequent images and was most consistent with a cystic benign prostatic hyperplasia nodule. A Prostate Imaging Reporting and Data System score of 2 was assigned.

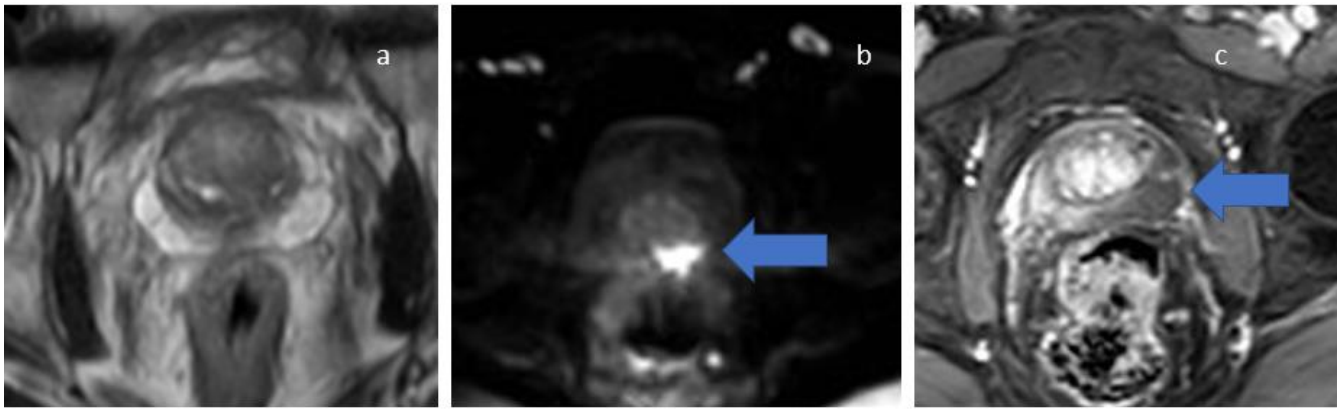

Figure 3. A 52-year-old man with increased prostate-specific antigen (PSA) level of 7.13 ng/mL and suspicious nodule on digital rectal examination in 2016. (a) T2-weighted axial image from the magnetic resonance imaging (MRI) of the prostate in 2016 did not show any suspicious lesion (Prostate Imaging Reporting and Data System score [PIRADS] 2). Systematic biopsy showed atypical small acinar proliferation, which was suspicious but not diagnostic for malignancy. PSA levels continued to increase, and a repeat MRI was performed in late 2018 when the PSA level was 23.81 ng/mL. (b). Axial diffusion-weighted MRI performed in 2018 showing an area of restricted diffusion in the left peripheral zone. (c) Corresponding late dynamic contrast-enhanced image showing early contrast wash-out from the lesion compared with the rest of the prostate gland. The lesion was >1.5 cm, and a PIRADS score of 5 was assigned. A repeat targeted biopsy revealed acinar adenocarcinoma, with Gleason score 3+3=6. The patient underwent radiotherapy and androgen deprivation therapy. Post-treatment PSA was 0.276 ng/mL.

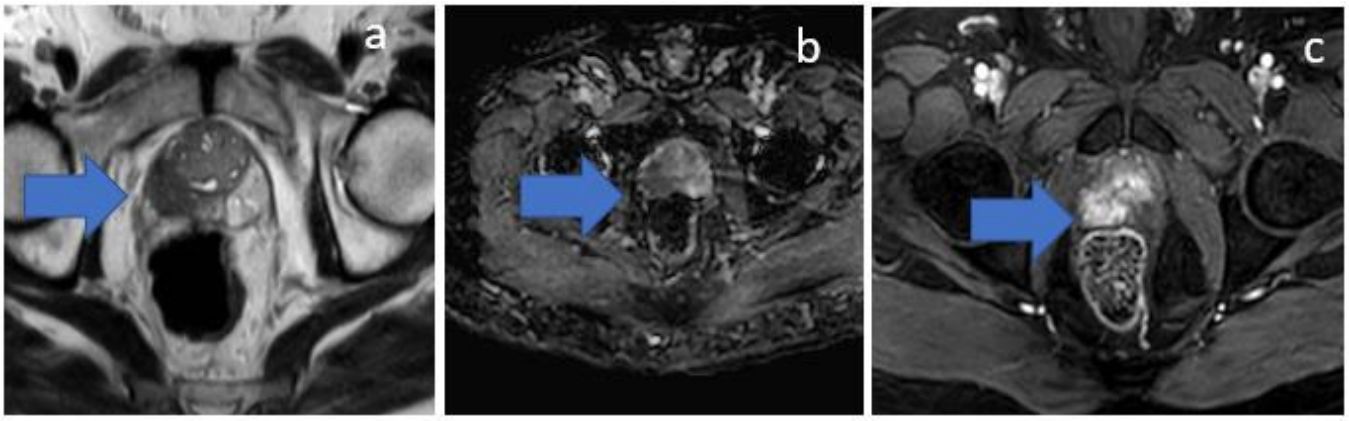

Figure 4. A 60-year-old man with increased prostate-specific antigen level of 22 ng/mL. (a) T2-weighted axial slice through the prostate gland showing a hypointense circumscribed lesion in the right lobe. (b) Apparent diffusion coefficient map showing corresponding low signal consistent with restricted diffusion. (c) Dynamic contrast-enhanced image showing early lesion contrast wash-in compared with the rest of the gland. Histology showed adenocarcinoma, with Gleason score 4+5.

The findings in the 52-year-old patient in Figure 3 further confirms this, as the MP-MRI was negative when the biopsy revealed no definite cancerous lesion, but both were positive when a cancerous lesion was present. These findings are comparable with results of Ahmed et al. (21), who found MP-MRI to have a sensitivity of 87% (95% CI, 83-90%) with a lower NPV of 72% (95% CI, 65-79%) for clinically significant cancer definition of Gleason score ≥3+4. High sensitivity and NPV of MP-MRI were also observed in a single-center prospective study in Australia by Thompson et al. (23) comparing MP-MRI in 344 men with template prostate mapping (TPM) biopsy (30 cores obtained) as the reference. A high sensitivity of 96% and NPV of 92% were obtained in this study while using a more robust reference test. These results are comparable to the

current study and add to the evidence of using MP-MRI as a triage tool before biopsy or to preclude a biopsy. Figure 4 is a good example of how MP-MRI can easily identify cancerous lesions that meet the PI-RADS diagnostic criteria as well as guide the biopsy for better yield. Cognitive fusion biopsy in the absence of MRI-guided biopsy is advantageous for lesions seen on MRI, as it allows targeted biopsies that have less morbidity than template biopsies and saves the pathologists' time, as there are fewer cores to be analyzed (24–26).

The specificity (47.8%; 95% CI, 38.5-55.7%) was the same as that obtained by Ahmed et al. (21), albeit with a narrower 95% CI (40–53%) than that in our study. Thompson et al. (23) obtained a much lower specificity of 36%. Interestingly, the systematic review and meta-analysis by de Rooij et al. (16) had a very high specificity of 88% (95% CI, 82-92%) and a sensitivity of 74%. However, the studies included in the review and meta-analysis were found to be highly heterogenous, with differences in reference tests and methods of analyses as well as some studies including Gleason scores as low as 4 and using PI-RADS version 1.

Although, typically, there is a tradeoff between sensitivity and specificity, a high specificity is important in a screening test (27). The low-specificity/high-false-positive rate in the current study is likely due to known pitfalls of MP-MRI, including BPH nodules and prostatitis mimicking prostate cancer (28). Twenty (57%) patients had BPH nodules seen on MRI that could mimic prostate cancer. Eight of the patients were confirmed to have BPH and/or prostatitis on histology, both of which are mimickers of prostate cancer. Some clinically significant lesions may also have been missed on TRUS-guided biopsy, which has been found to miss clinically significant cancer that is diagnosed on a repeat TRUS-guided biopsy or following TPM biopsy. In the Prostate MR Imaging Study (PROMIS) (21), TRUS-guided biopsy missed 119 clinically significant cancers out of 576 TRUS biopsies done; these were all picked up on TPM biopsy.

In the current study, 35 false-positive results were found. Further assessment of the 35 false-positive results was done to establish any emerging trends. Of 35 patients, 5 had been assigned PI-RADS 3 as a final diagnosis, whereas 7 had at least one of the radiologists assign a PI-RADS 3 category. PI-RADS 3 lesions may significantly affect the results because some of the lesions assigned this category end up as clinically significant cancer on histology, whereas some are negative. Unfortunately, some lesions have equivocal characteristics, and there is no sure way of predicting whether to biopsy or not. It would be a worthwhile suggestion to have a management system for the PI-RADS 3 lesions; for example, a multidisciplinary meeting to review the images and histology results before deciding on a treatment plan for each patient (24,29). The subsequent steps may include active surveillance, repeat targeted biopsy, or repeat MRI in cases of prostatitis.

The MP-MRI PPV, 60.87% (95% CI, 52.5-69.3%), was reasonable and comparable with that found by Ahmed et al. (69%; 95% CI, 64-73%) (21). Thompson et al. (23) had a PPV of 52%. The differences in PPVs are most likely due to the differences in prevalence of clinically significant prostate cancer of 47% (95% CI, 39.6-56.6%) in this study compared with 57% (95% CI, 53-62%) in the study of Ahmed et al. Data on prevalence rates of prostate cancer in the sub-Saharan African population would have been helpful for better PPV comparisons. The wider 95% CIs in this study compared with those in the study of Ahmed et al. are most likely due to a smaller sample size of 133 patients compared with 576 in the former study. In literature, differences in PPVs of different studies have also been attributed to variations in the patient population studied, the definition of a positive MRI, and the reference test used (23).

The interobserver agreement of the two readers in this study was 0.59, which is moderate. This was comparable to PROMIS, where 132 patients had "blinded double reporting" of the MP-MRI with similar dichotomization of the MP-MRI categories (1-2, negative; 3-5, positive) as in our study and found moderate agreement with a kappa statistic of 0.5.

This study has a few limitations. First, it was done retrospectively with a relatively small sample size compared with similar studies done elsewhere. The study being retrospective introduced selection bias, as the selected cases were already suspected to have

prostate cancer necessitating a biopsy. Second, the reference test (TRUS-guided biopsy) is less than ideal and has a number of pitfalls, including missing clinically significant lesions and has been shown to have a false-negative rate of 15-45% (21,25). The pitfalls of MP-MRI with benign pathology such as BPH nodules and prostatitis mimicking prostate cancer as well as post-biopsy hemorrhage result in false-positive findings. These contributed to some of the mismatch between MP-MRI and histology findings.

Conclusion

MP-MRI has both high sensitivity and NPV, validating its use in pre-biopsy evaluation of men of African descent at risk of prostate cancer to safely avoid unnecessary prostate biopsy, with its complications, in men unlikely to have clinically significant disease, to detect clinically significant cancer, and to guide TRUS-guided biopsy of suspicious lesions. Addition of MP-MRI in clinical pathways for prostate cancer evaluation is recommended in this population.

Declaration of interests

The authors declare no conflict of interest.

Author contributions

MKO led in writing the original draft. All other tasks were shared equally.

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