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PI-RADS Committee Position on MRI Without Contrast Medium in Biopsy Naive Men with Suspected Prostate Cancer: A Narrative Review

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Abstract

The steadily increasing demand for diagnostic prostate MRI has led to concerns regarding the lack of access to, and the availability of qualified MRI scanners, and sufficiently experienced radiologists and radiographers/technologists to meet the demand. Solutions must enhance operational benefits without compromising diagnostic performance, quality and delivery of service. Solutions should also mitigate risks, such as decreased reader confidence and referrer engagement. One approach may be the implementation of MRI without the use gadolinium-based contrast medium (also referred to as "biparametric MRI"), but only if certain prerequisites such as high-quality imaging, expert interpretation quality, and availability of patient recall or on-table monitoring are mandated. Alternatively, or in combination, a clinical risk-based approach could be used to decide on protocol selection, specifically which biopsy naïve man needs MRI with contrast (multiparametric MRI). There is a need for prospective studies where biopsy decisions are based upon MRI without contrast. Such studies must define clinical and operational benefits and identify which patient groups can be scanned successfully without contrast. These higher quality data are needed before the PI-RADS Committee can make evidence-based recommendations about MRI without contrast as an initial diagnostic approach for prostate cancer work-up.

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1. Introduction

In prostate cancer diagnosis, it is important to distinguish men with clinically significant disease from those with insignificant disease. Men with significant disease are more likely to benefit from treatment, while those with insignificant disease will most likely suffer no harm from their disease [1]. Clinical benefit derives from either a timely diagnosis and appropriate treatment of prognostically significant disease, or the avoidance of clinical harms including over-diagnosis, over-treatment, and unnecessary biopsies and their associated risks of complications. The MRI approach in biopsy naïve men can deliver both benefits: from early diagnosis in the case of MRI-positive results of significant cancers, to potential biopsy avoidance resulting from MRI-negative results, leading to decreased rates of indolent cancer detection [2].

The demand for prostate MRI and associated waiting times are increasing in many countries [3-5]. This mandates expanding diagnostic capacity and increasing patient throughput. Concerns have been raised about the lack of access to PI-RADS compliant MRI scanners, as well as of enough experienced radiologists and radiographers or technologists to meet this growing demand. Other impediments include inconsistencies of image quality, lack of objective diagnostic quality metrics and the challenges of managing the higher demand and volume of examinations [6]. Solutions must mitigate the resulting risks which include decreased reading confidence of radiologists, and diminished diagnostic performance [7], while enhancing operational benefits and enabling costs savings if possible.

In this paper, we focus on the potential role of MRI without the use of gadolinium-based contrast medium (non-contrast MRI) as one solution to meet the increased demands in biopsy naïve men with suspicion of prostate cancer. We compare the non-contrast MRI (also referred to as “biparametric MRI” or “bpMRI” in other publications) with the approaches of standard multiparametric MRI (MRI with dynamic contrast-enhancement (DCE) as described in PI-RADS v2.1 [8]), and discuss operational aspects and impacts on radiological image assessments and diagnostic performance. Clinical risk groups are commonly used to decide on the need for prostate biopsy in the setting of opportunistic screening. We therefore put forward the concept of risk grouping for directing the need to administer contrast medium in biopsy naïve men.

Therein, the potential added value of the dynamic contrast-enhanced MRI (DCE-MRI) sequence in different risk scenarios in biopsy naïve men is discussed in detail.

2. Impacts of non-contrast MRI on clinical practice

2.1. Impacts on operations

Non-contrast MRI can shorten examination times and pre-MRI preparations, with no contrast-medium related precautions, potentially enabling increased patient throughput (*Table 1*). Moreover, MRI protocols without contrast injections may be preferred by patients, reducing patient discomfort, adverse effects and 'in-the-scanner' time [9]. Excluding the DCE-MRI sequence from MRI examinations substantially decreases the overall costs because contrast medium is not used, radiologist's presence is not required, injection apparatuses and accessories are not needed, and shorter scanner times are enabled [10]. These operational benefits need to be carefully weighed against the impacts on radiological image assessments and diagnostic performance [7].

2.2. Impacts on radiological image assessments

Negative MRI cases can be identified by using T2-weighted (T2W) and diffusion-weighted imaging (DWI) criteria alone according to PI-RADS v2.1, and DCE-MRI is not routinely needed to call an MRI examination negative (PI-RADS scores 1 and 2). Negative contrast MRI scans are estimated to account for up to 30-40% of all intermediate- to high-risk biopsy naïve men coming to MRI examinations [11, 12]. This proportion is even higher in lower-risk men [13]. Broadly, the proportion of negative non-contrast MRI [14-17] is of similar magnitude to contrast MRI studies [18-20] when adjusted for disease prevalence.

Most MRI positive cases can also be identified by using T2W and DWI criteria alone, especially for larger tumors assigned to the PI-RADS 5 category and a substantial proportion of PI-RADS 4 lesions also (*Figure 1*). There is a role for DCE-MRI for detecting small cancers which are less obvious or occult on T2W and DWI [8, 21] or when DWI images are degraded by hip prostheses. The presence of focal contrast enhancement can increase reader confidence, helping less experienced readers call MRI scans positive [22-24]. Limited literature indicates that contrast

medium upgraded lesions are likely to be cancers, although the proportion of ISUP grade ≥3 is not well documented. [21, 24].

The formal codified role of DCE-MRI within PI-RADS v2.1 is limited to, (1) the characterization of category 3 lesions in the peripheral zone of the prostate gland, where DCE-MRI features affect the final PI-RADS category assignments, and (2) the characterization of PI-RADS 3 lesions in the transition zone when there are artefacts on DWI [8]. When a peripheral zone category 3 lesion shows focal enhancement, it is upgraded to a PI-RADS 4 category lesion (*Figure 2*). Readers should note that upgraded PI-RADS 3 lesions (PI-RADS 3+1) are distinct from native PI-RADS 4 category lesions in terms of the prevalence of clinically significant prostate cancer (csPCa) [25-27]. Unfortunately, there is no clear documentation on the frequency of upgrading of PI-RADS 3 lesions by DCE-MRI. Zawaideh et al noted increases in the number of positive MRI assessments when using the contrast MRI approach (non-contrast MRI: n=132 cases, contrast MRI: n=143 cases; ratio 1.08) suggesting an 8% increase for their Likert system (*Table 2*) [24]. It is estimated that up to 80% of the administered contrast medium has no effect on the final PI-RADS category assignments, and therefore may not have major impacts on the clinical decision regarding the need for biopsies [24, 28].

The absence of the DCE-MRI sequence can have an impact on reading performance (identification and demarcation) in all zones of the prostate gland, especially for less experienced readers (*Figure 3*) [22-24, 27]. In a reading performance study, inexperienced readers performed significantly worse with non-contrast MRI compared to contrast MRI for the same fixed number of cases [22]. For readers who had cumulatively interpreted 300 cases, the contrast vs. non-contrast MRI sensitivities were 0.91 vs. 0.58 ($p < 0.01$) and AUC were 0.86 vs. 0.73 ($p=0.01$), while readers who had read 1000 cases, had comparable sensitivities of 0.91 vs. 0.96, and AUC 0.86 vs. 0.93 ($p \geq 0.10$). Although education, training and histological feedback are critical for performance improvements, these data suggest that the use of non-contrast MRI may be most suited for expert readers, and that less experienced readers may need and rely upon DCE-MRI to boost their diagnostic confidence and performance [24].

The absence of DCE-MRI sequence may also lead to greater uncertainty with increases in the proportion of indeterminate cases going for biopsies, even for expert readers, regardless of

the reading system used. In an in-depth analysis of diagnostic performance studies, with direct head-to-head comparisons between non-contrast and contrast MRI for cancer detection, we found only 6 studies [24, 29-32] in the clinical diagnosis setting (referenced to biopsies) and 3 studies [26, 33, 34] referenced to radical prostatectomy specimens (*Table 2*). In the diagnostic setting, the prospective, multicenter 4M study [30] noted more indeterminate PI-RADS 3 category cases for non-contrast MRI approaches (11% (n=70) for uniplanar and 8% (n=49) for multiplanar non-contrast MRI) than for contrast MRI (6% (n=40)) for two highly expert readers. This effect was also noted for the Likert systems (alternatives to PI-RADS assessment, which are more subjective, based on reporter experience, also incorporating clinical parameters) used in the secondary analysis of the prospective multicenter PROMIS study [29], where the number of equivocal Likert 3 scores increased from 27% (n=136) of patients using contrast MRI, to 32% (n=158) using non-contrast MRI (p = 0.031). In a prospective single-center multi-reader study [24], the number of equivocal Likert 3 scores increased from 8% (n=22) using contrast MRI to 17% (n=45) using non-contrast MRI. Although contrast MRI was found to be helpful for 28% of score determinations, readers would only have recalled one out of 10 patients (11%) for DCE-MRI sequence, mainly to assess indeterminate lesions in the peripheral zone. Only one retrospective single-center, single reader study [31] has noted that Likert 3 category cases decreased when using the non-contrast MRI approach (from 29% (n=69) with contrast to 20% (n=48) without contrast). The retrospective study design and high non-contrast MRI experience of the reader are biases.

More indeterminate cases could have the effect of undermining the confidence of MRI utility amongst referring physicians deciding on who, and which lesions, to biopsy. Referring physicians often prefer binary 'yes/no' answers. Therefore, the proportion of PI-RADS 3 cases should be low. It should be noted, however, that the proportion of PI-RADS 3 lesions is dependent on disease prevalence, and the composition of the patient population. For a disease prevalence of csPCa of 40% (range 4 to 65%), the average literature PI-RADS 3 proportion is approximately 17% (range 6 to 46%) [28] within some expert centers achieving lower (<10%) PI-RADS 3 proportions [20, 35, 36].

2.3. Impacts on diagnostic performance

Multiple systematic reviews and meta-analyses have been conducted in mixed populations comparing the diagnostic performance of non-contrast and contrast MRI [37-41]. Four analyses [37-40] showed that the detection rates for all cancers are marginally increased with the use of DCE-MRI, whereas another did not [41] (*Table 3*). The meta-analysis of Niu et al [40], comparing head-to-head studies for the detection of all prostate cancers, showed that contrast MRI had a modestly higher pooled sensitivity (0.85 (95% CI: 0.78–0.93)) than non-contrast MRI (0.80 (0.71-0.90); P=0.01) due to trends observed in 7 of the 11 studies included. However, the pooled specificity values were not different (contrast MRI, 0.77 (0.58–0.95), non-contrast MRI, 0.80 (0.64–0.96); P=0.82).

It seems as though contrast enhancement has no or only marginal effects on the diagnostic performance for the detection of clinically significant cancers [38, 39]. In a sub-analysis of direct head-to-head comparison studies of non-contrast and contrast MRI focusing on csPCa only, Alabousi et al [38] showed pooled summary statistics of 6 studies without significant difference for sensitivity (non-contrast MRI: 0.91 (0.82–0.96); contrast MRI: 0.92 (0.91–0.94)) or specificity (non-contrast MRI: 0.73 (0.37-0.92); contrast MRI: 0.65 (0.33–0.87)) (*Table 3*). Woo et al. showed similar results [37]. In the Cochrane sub-analysis [12], the detection of ISUP grade group ≥2 cancers for contrast MRI (16 studies; 1.18 (1.05-1.33)) was higher than for non-contrast MRI (6 studies; 1.03 (0.91-1.17)), when related to systematic biopsies, however, without significant difference (*P*=0.23).

We advise caution on taking pooled test accuracies at face value because of the considerable heterogeneity amongst the studies evaluated (*Table 3*). The mixing of reference standards for determining diagnostic metrics is a serious hazard for adoption into clinical diagnostic practice. Similarly, MRI data obtained after the cancer diagnosis for treatment guidance, will differ from MRI data in the diagnostic work-up of patients. Differences in review designs are also impactful; some reviews have included studies with either non-contrast MRI or contrast MRI results, others including only studies on head-to-head comparisons of non-contrast MRI and contrast MRI results. The mixing of populations amongst the included studies is of particular concern when recommendations are being made about the diagnostic use of non-contrast MRI for biopsy naïve men. We have only seen this evaluated specifically in the head-to-

head comparison review of Woo et al [37]: a sub-analysis in biopsy naïve men revealed only 3 studies, showing pooled summary statistics without significant difference (p=0.36) for sensitivity (non-contrast MRI: 0.63 (0.51–0.75); contrast MRI: 0.69 (0.58–0.81) or specificity (non-contrast MRI: 0.94 (0.90–0.97); contrast MRI: 0.89 (0.85–0.94).

Systematic analyses have also noted that the definition of clinically significant cancer vary widely between studies, as do the methods used for image evaluations (e.g. clinical Likert and PI-RADS systems). Other sources of heterogeneity also significantly affect disease detection sensitivity including the type of coils used, magnetic field strength, use of ADC (apparent diffusion coefficient)-maps and ultra-high b-values, patient enrollment, and reader blinding [12, 39]. Importantly, in all direct comparison studies, biopsy decisions are based on contrast MRI results, and we cannot know the relative diagnostic performance of non-contrast MRI in comparison to contrast MRI. Taken together, the pooled data showing statistical non-inferiority can only be considered being as broadly supportive of the non-contrast MRI approach, but the heterogeneity undermines the scientific strength of the non-contrast MRI observations, and its applicability for biopsy-naïve men. Better designed, randomized prospective trials are needed where biopsy decisions are made using non-contrast MRI separate from using contrast MRI, within uniform populations at usual risk of prostate cancer, to increase confidence in the non-contrast MRI-directed biopsy approach for biopsy naïve men suspected to have prostate cancer.

Having noted the serious study limitations above, support for the non-contrast MRI approach comes from the PROMIS study where all men underwent 5 mm transperineal template mapping biopsies [29]. In a paired validation analysis, equivalent diagnostic metrics were realized for ISUP grade ≥2 cancers for non-contrast and contrast MRI readings. For non-contrast MRI and contrast MRI respectively, the sensitivity (89% and 88%), specificity (44% and 44%), positive predictive value (69% and 69%), and negative predictive value (74% and 72%) were similar. The same was noted for alternative histopathology definitions of significant disease (Gleason score ≥4 + 3 or any cancer core length ≥6 mm).

Of note, diagnostic performance is a balance between sensitivity (low false negatives) and specificity (low false positives). The reported data by Tamada et al regarding inter-reader diagnostic performances in a lesion-based analysis showed increased sensitivity at the expense

of decreased specificity for MRI with contrast, contrasting increased specificity at the expense of decreased sensitivity for MRI without contrast [27].

These data lead us to conclude that only a minority of men who are upgraded from the PI-RADS 3 to PI-RADS 4 category by contrast MRI have cancers that need to be detected immediately. That is, the majority of the additional cancers detected are often ISUP grade 1 and microfocal ISUP grade 2 tumors, corresponding to their respective population prevalences [31, 42, 43]. The presence of focal enhancement does not consistently differ between tumor grades in peripheral zone cancers [44]. So, while DCE-MRI helps detect more lesions, the impact on the detection of aggressive high-grade cancers with primary Gleason pattern 4 (ISUP grade ≥ 3) is not well documented.

3. Using non-contrast MRI as the default approach

As the diagnostic performance of non-contrast MRI does not appear to be inferior to contrast MRI (with caveats), and the radiological image assessments and biopsy decisions are not hampered for the majority of biopsy-naïve men (*Table 2 and 3*), a shift towards non-contrast MRI as the default initial approach in biopsy naïve men may be adopted. However, we need to attach some important prerequisites where we to adopt this approach (*Table 4*).

3.1. High-quality imaging (1)

While within PI-RADS, the DCE-MRI sequence is only needed to classify an indeterminate lesion in the peripheral zone (PI-RADS 3), it can also be used informally to exclude and to detect lesions as alluded above. These diagnostic “safety-net” or “back-up sequence” uses can improve reader confidence and might allow otherwise missed lesions to be detected when there is insufficient image quality due to artifacts or inadequate signal-to-noise ratio on DWI (*Figure 4*) [8]. MR image quality is therefore of paramount importance and should always be assessed as part of routine non-contrast MRI reporting, with statements indicating whether the image quality is sufficient for ‘ruling-in’ and ‘ruling-out’ clinically significant cancers, as recently suggested by de Rooij et al [6] and Giganti et al [45].

Given the documented impacts of technical factors on the sensitivity of non-contrast MRI for ISUP grade group ≥2 cancers described in all systematic analyses, the minimal requirements

for data acquisitions in the PI-RADS v2.1 guidelines need adjusting for non-contrast and contrast MRI examinations [8]. That is, we will need to set higher technical standards, to obtain impeccable T2W/DWI quality [46, 47]. While these requirements apply to both non-contrast and contrast MRI, optimal image-acquisitions and pre-MRI preparations, are necessary on the premise that there is likely to be a degradation of non-contrast MRI test performance in clinical practice, compared to its use at expert centers. Initiatives to improve image quality must be undertaken by all stakeholders, from MRI manufacturers, physicists, radiologists and organizations such as European Imaging Biomarkers Alliance (EIBALL) and Quantitative Imaging Biomarker Alliance (QIBA).

3.2. High reader expertise (2)

Accurate detection and characterization of cancer suspicious foci has a learning curve that can be shortened with education, training and practice expertise. The suggested threshold of cases for reliable non-contrast MRI interpretation previously discussed [22, 23] set a high-bar for its successful use, which may require the division of radiologists who can and who should not interpret non-contrast MRI examinations, according to agreed local practice. Less experienced readers will negatively impact the diagnostic performance of MRI, affect the confidence and adoption of non-contrast MRI by urologists, and on influence biopsy decisions. Therefore, centers utilizing non-contrast MRI may consider concentrating the MRI-directed diagnostic work-up around dedicated expert prostate cancer physicians, working in multidisciplinary teams [48, 49].

3.3. Adjustments of biopsy decision thresholds according to clinical risk (3)

The non-contrast MRI approach may require a higher PI-RADS threshold for defining test positivity, to minimize over-diagnosis in low disease prevalence settings [1]. When there is low disease prevalence, the non-contrast PI-RADS 4-5 cut-off appears better correlated to ISUP grade group ≥2 disease detection, achieving a better balance between sensitivity and specificity with less false positive cases [50]. However, the non-contrast PI-RADS threshold for biopsy in men with elevated PSA or in those with abnormal digital rectal examinations is likely to be the same as when using contrast MRI (that is, PI-RADS 3-5). Refinements of the threshold for biopsy in non-contrast MRI examinations using PSA-density, for men with elevated PSA values are also emerging [16, 20, 51, 52]. Changing biopsy thresholds in the way described will have impacts on reader and

diagnostic performance of non-contrast MRI. These will require redocumentation for benchmarking purposes.

3.4. Reader performance assessments and benchmarking (4)

Reader performance assessments in MRI-directed diagnostic work-ups are essential regardless of the MRI technique used. Where non-contrast MRI is the default strategy, the need for regular peer review is even more pressing, with checking of inter- and intra-observer variability and/or within multidisciplinary meetings, where consistency and discrepancy between non-contrast MRI, biopsy, and histological outcomes can be monitored.

In the absence of any biopsy for PI-RADS 1-2 categories, the negative predictive value cannot serve as a suitable metric for assessing reader performance for daily practice, as 'false-negative results' will not be determined on an ongoing and timely basis. Comparative diagnostic center cancer detection rates in MRI-positive men are also problematic because of the impact of disease prevalence on MRI-positivity between centers [53]. Inter-reader PI-RADS proportions and cancer detection rates within a given center maybe used to monitor performance against peers [54, 55]. Interobserver agreement estimates are available for non-contrast and contrast MRI [30, 32, 56]. However, currently, we cannot determine whether non-contrast or contrast MRI has better interobserver agreement.

In order to undertake new benchmarking, re-documentation on PI-RADS proportions and likely diagnostic yields will be needed for non-contrast MRI, where biopsy decision making is based upon non-contrast MRI. These are needed for different image defined biopsy thresholds and for different disease prevalences [17, 57]. Cancer detection rate benchmarking against literature values may not be appropriate due to differences in disease prevalence and patient characteristics, unless appropriate adjustments are made [17]. Higher cancer detection rates can be expected when disease prevalence is high [58], with corresponding alterations in the proportion of negative, equivocal and positive MRI results.

3.5. Diagnostic safety-net: patient recalls or on-table monitoring (5)

Formally instituting patient recalls to imaging centers for DCE-MRI sequences will become necessary as non-contrast MRI examinations are increasingly applied, as part of the delayed 'diagnostic safety-net' recall of patients. This should be done when there is insufficient quality of

T2W or DWI images (*Figure 4*), and in indeterminate cases (*Figure 2*) [59]. Alternatively, direct monitoring when the patient is on the scanner could minimize these recalls. However, this would be logistically challenging and probably not cost-efficient from a scheduling perspective. This may in the future be addressed by artificial intelligence algorithms that will ensure high quality acquisitions. It should be borne in mind that the 'diagnostic safety-net' use of DCE-MRI may yield enhancing lesions that are imperceptible on T2W or DWI (*Figure 5*) but as already noted, the lesions revealed may not represent clinically significant cancers, thus adversely impacting on false positivity rates.

3.6. Monitoring or follow-up safety-net (6)

As with contrast MRI, the 'monitoring or follow-up safety-net' after low likelihood findings on non-contrast MRI in intermediate- and high-risk biopsy-naïve men should also be undertaken, in men avoiding immediate systematic biopsies. The 'follow-up safety-net' includes clinical and laboratory assays and repeated imaging as per local clinical practice and consistent with clinical goals for individual patients as discussed in more detail below (section 4.2).

4. Pre-MRI risk grouping for deciding on the use of DCE-MRI

In the hypothesized clinical scenario of non-contrast MRI adoption as the default diagnostic strategy, DCE-MRI would be primarily abandoned for all referred patients. Contrast medium use would be reserved for PI-RADS 3-4 cases where there is potential added diagnostic value including biopsy guidance (*Figure 6a*). To overcome the challenges and bothersome recalls needed to do this successfully, an alternative scenario of pre-MRI risk assessments could be envisioned (*Figure 6b*). Grouping men into low-, intermediate-, and high-risk categories, using the proven clinical risk assessment calculators/nomograms already in use for biopsy decisions by urologists, can enable the selection of men in whom DCE-MRI may or may not be contributory for MRI assessments, and for deciding on biopsy strategies (*Figure 7*).

4.1. Men at low-risk

In men with a low-risk of csPCa (e.g. in general population screening), the aim of MRI is (a) to rule-out clinically significant disease (tumors that should not be missed; ISUP grade group 3-5 disease), and (b) importantly to minimize over-diagnoses in the setting of a high background prevalence of

ISUP grade 1 cancers in older men [1]. Reduction of over-diagnosis remains a major clinical priority for biopsy-naive men as indicated by the US Preventive Services Task Force 2017 [60].

A substantial proportion of low-risk men will have a negative MRI (PI-RADS 1-2) [11, 12] which can be defined using non-contrast MRI alone. Non-contrast MRI is, therefore, a reasonable option in biopsy naive men who are at low-risk and are concerned about over-diagnoses. In these men, non-contrast MRI may be adequate to exclude clinically significant disease using a higher threshold for biopsy (PI-RADS 4-5) as shown recently by the PROSTAGRAM screening study where the disease prevalence was 4% [50].

4.2. **Men at intermediate- and high-risk**

Men at intermediate-risk may undergo contrast MRI as the default approach (*Figure 7*). As previously mentioned, DCE-MRI has the potential for additional value in the peripheral zone to improve the risk stratification of indeterminate lesions (PI-RADS 3) and for biopsy planning for smaller (PI-RADS 4) lesions. Radiologists benefit from DCE-MRI use because of improved reading confidence and because of fewer indeterminate cases, rather than for the reasons of improved diagnostic performance (*Table 2*). In these men, DCE-MRI may guide tumor biopsy approaches. For discrete focal lesions, targeted biopsies may be sufficient, but for lesions with peri-tumoral penumbral enhancement, a focal saturation approach (MRI-directed biopsies of the lesion and peri-lesional region) may enable improved pathological risk stratification [20].

Biopsy-naive men with strong family history, known genetic predisposition, elevated serum and urinary genomic scores, and men with higher than average risk calculator scores for significant cancer, may benefit from contrast MRI as the default option. For these men, biopsy avoidance is not a clinical priority, but the detection and volumetric estimates of clinically significant disease are important to effect timely curative therapies. For these men, a pre-MRI risk assessment mandates the use of contrast MRI.

In men at persistent (higher) risk, such as those with prior negative biopsies with unexplained persistent elevated PSA levels, suspicious prior histology (e.g. high-grade prostate intraepithelial neoplasia or atypical ductal hyperplasia), and in active surveillance patients being evaluated for fast PSA doubling times or changing clinical or pathologic status, contrast MRI is also preferred. For men who have previously undergone a non-contrast MRI examination that did

not show suspicious findings, and who remain at persistent suspicion of harboring csPCa, the clinical priority for subsequent MRI scans is to not miss csPCa; thus, the preferred option is histological evaluations with or without re-imaging, using contrast MRI.

To reduce the need for all men with intermediate- and high-risk requiring DCE-MRI, on-table MRI monitoring (by trained technologists, radiologists, machine learning software) of images may allow contrast medium to be omitted when larger volume tumors are present, and when there is already sufficient information for biopsy planning and staging. Some investigators are now using other biomarkers such as PSA-density in men with elevated PSA levels, to identify men at higher risk after a negative or indeterminate MRI [51]. Prostate volume assessments and PSA-density calculations are easily done after the T2W images are acquired, enabling the personalized use of contrast medium for men with higher PSA-densities.

4.3. **Men with clinical locally advanced disease**

Men who are highly likely to have significant prostate cancer based on very elevated serum PSA levels accompanied by abnormal digital rectal examinations suggesting locally advanced disease (high-risk, locally advanced prostate cancer), are unlikely to derive clinical benefits from contrast MRI use for diagnosis [61]. Most of these men have larger tumors that are easily staged, and biopsy planned by using non-contrast MRI. Contrast enhancement can be helpful for some men for staging (bladder neck invasion, seminal vesicle invasion) and sometimes for differential diagnosis of PI-RADS 4 and 5 lesions (e.g. high-grade PIN, prostatitis).

5. Consensus statements

(1) Non-contrast MRI represents a potential solution for meeting the increasing demand for MRI in the prostate cancer diagnostic workup. The advantages and disadvantages for operational workflows, radiological assessments, and diagnostic performance must be weighed carefully, taking into account the likelihood of clinically significant disease being present and the clinical priorities of patients and their referrers.

(2) Optimal image acquisition and data interpretations are mandatory on the premise that there is likely to be a degradation of non-contrast MRI performance in clinical practice. When non-

contrast MRI examinations are undertaken, the proportion of men in the indeterminate category will likely increase.

(3) Instituting patient recalls should be pursued in cases when there is insufficient image quality and in indeterminate cases, where contrast enhancement may add value to mitigate the risks of decreased MRI reading confidence or inaccurate diagnoses. As an alternative, on-table monitoring of image quality and/or tailoring the need for contrast enhancement according to patient risk can be explored.

(4) Higher quality data are needed before the PI-RADS Committee can make evidence-based recommendations about MRI without contrast as an initial diagnostic approach for prostate cancer work-up. Specifically, there is a need for prospective, comparative studies where biopsy decisions are based upon MRI with and without contrast in different patients. Such studies must define both clinical and operational benefits and identify which patient groups can be scanned successfully without contrast.

(5) The current analysis indicates the need to have both non-contrast MRI and contrast MRI approaches available for prostate cancer diagnosis. Greater evidence is needed to precisely define which patient groups benefit from contrast enhancement and who can safely avoid it.

References

1. Welch HG, Albertsen PC. Reconsidering Prostate Cancer Mortality - The Future of PSA Screening. *The New England journal of medicine* 2020; 382:1557-1563
2. Padhani AR, Weinreb J, Rosenkrantz AB, Villeirs G, Turkbey B, Barentsz J. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions. *European urology* 2019; 75:385-396
3. Rosenkrantz AB, Hemingway J, Hughes DR, Duszak R, Jr., Allen B, Jr., Weinreb JC. Evolving Use of Prebiopsy Prostate Magnetic Resonance Imaging in the Medicare Population. *The Journal of urology* 2018; 200:89-94
4. Oberlin DT, Casalino DD, Miller FH, Meeks JJ. Dramatic increase in the utilization of multiparametric magnetic resonance imaging for detection and management of prostate cancer. *Abdominal radiology (New York)* 2017; 42:1255-1258
5. Renard-Penna R, Rouviere O, Puech P, et al. Current practice and access to prostate MR imaging in France. *Diagnostic and interventional imaging* 2016; 97:1125-1129
6. de Rooij M, Israel B, Tummers M, et al. ESUR/ESUI consensus statements on multi-parametric MRI for the detection of clinically significant prostate cancer: quality requirements for image acquisition, interpretation and radiologists' training. *European radiology* 2020;
7. Padhani AR, Schoots I, Villeirs G. Contrast Medium or No Contrast Medium for Prostate Cancer Diagnosis. That Is the Question. *Journal of magnetic resonance imaging : JMRI* 2020;
8. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *European urology* 2019; 76:340-351
9. Fox-Rawlings S, Zuckerman D. NCHR Report: The Health Risks of MRIs with Gadolinium-Based Contrast Agents. In: *http://wwwcenter4researchorg/health-risks-of-gbcas/*: National Center for Health Research, 2019
10. Mowatt G, Scotland G, Boachie C, et al. The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation. *Health technology assessment (Winchester, England)* 2013; 17:vii-xix, 1-281
11. Kasivisvanathan V, Stabile A, Neves JB, et al. Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-analysis. *European urology* 2019; 76:284-303
12. Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *The Cochrane database of systematic reviews* 2019; 4:CD012663
13. Schoots I, Padhani A. Risk-adapted biopsy decision making based on prostate MRI and PSA-density, for enhanced avoidance of biopsies in biopsy-naïve men for prostate cancer diagnosis. *European urology* 2020; (in submission)

14. Jambor I, Verho J, Ettala O, et al. Validation of IMPROD biparametric MRI in men with clinically suspected prostate cancer: A prospective multi-institutional trial. *PLoS medicine* 2019; 16:e1002813
15. Boesen L, Norgaard N, Logager V, et al. Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for Prostate Cancer in Biopsy-Naive Men: The Biparametric MRI for Detection of Prostate Cancer (BIDOC) Study. *JAMA Netw Open* 2018; 1:e180219
16. Hansen NL, Barrett T, Kesch C, et al. Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naive men with suspicion of prostate cancer. *BJU international* 2018; 122:40-49
17. Knaapila J, Jambor I, Ettala O, et al. Negative Predictive Value of Biparametric Prostate Magnetic Resonance Imaging in Excluding Significant Prostate Cancer: A Pooled Data Analysis Based on Clinical Data from Four Prospective, Registered Studies. *Eur Urol Focus* 2020; 14:30106-30101
18. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *New England Journal of Medicine* 2018; 378:1767-1777
19. Rouviere O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *The lancet oncology* 2019; 20:100-109
20. van der Leest M, Cornel E, Israel B, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. *European urology* 2019; 75:570-578
21. Chatterjee A, Tokdemir S, Gallan AJ, et al. Multiparametric MRI Features and Pathologic Outcome of Wedge-Shaped Lesions in the Peripheral Zone on T2-Weighted Images of the Prostate. *AJR Am J Roentgenol* 2019; 212:124-129. doi: 110.2214/AJR.2218.19742. Epub 12018 Nov 19747.
22. Gatti M, Faletti R, Calleris G, et al. Prostate cancer detection with biparametric magnetic resonance imaging (bpMRI) by readers with different experience: performance and comparison with multiparametric (mpMRI). *Abdominal radiology (New York)* 2019; 44:1883-1893
23. Di Campli E, Delli Pizzi A, Seccia B, et al. Diagnostic accuracy of biparametric vs multiparametric MRI in clinically significant prostate cancer: Comparison between readers with different experience. *European journal of radiology* 2018; 101:17-23
24. Zawaideh JP, Sala E, Shaida N, et al. Diagnostic accuracy of biparametric versus multiparametric prostate MRI: assessment of contrast benefit in clinical practice. *European radiology* 2020;
25. Roh AT, Fan RE, Sonn GA, Vasanawala SS, Ghanouni P, Loening AM. How Often is the Dynamic Contrast Enhanced Score Needed in PI-RADS Version 2? *Curr Probl Diagn Radiol* 2020; 49:173-176
26. Choi MH, Kim CK, Lee YJ, Jung SE. Prebiopsy Biparametric MRI for Clinically Significant Prostate Cancer Detection With PI-RADS Version 2: A Multicenter Study. *AJR American journal of roentgenology* 2019; 212:839-846

27. Tamada T, Kido A, Yamamoto A, et al. Comparison of Biparametric and Multiparametric MRI for Clinically Significant Prostate Cancer Detection With PI-RADS Version 2.1. *Journal of magnetic resonance imaging : JMRI* 2020:e27283
28. Maggi M, Panebianco V, Mosca A, et al. Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus* 2019;
29. Bosaily AE, Frangou E, Ahmed HU, et al. Additional Value of Dynamic Contrast-enhanced Sequences in Multiparametric Prostate Magnetic Resonance Imaging: Data from the PROMIS Study. *European urology* 2020;
30. van der Leest M, Israel B, Cornel EB, et al. High Diagnostic Performance of Short Magnetic Resonance Imaging Protocols for Prostate Cancer Detection in Biopsy-naive Men: The Next Step in Magnetic Resonance Imaging Accessibility. *European urology* 2019;
31. Junker D, Steinkohl F, Fritz V, et al. Comparison of multiparametric and biparametric MRI of the prostate: are gadolinium-based contrast agents needed for routine examinations? *World journal of urology* 2019; 37:691-699
32. Kuhl CK, Bruhn R, Kramer N, Nebelung S, Heidenreich A, Schrading S. Abbreviated Biparametric Prostate MR Imaging in Men with Elevated Prostate-specific Antigen. *Radiology* 2017; 285:493-505
33. Thestrup KC, Logager V, Baslev I, Moller JM, Hansen RH, Thomsen HS. Biparametric versus multiparametric MRI in the diagnosis of prostate cancer. *Acta Radiol Open* 2016; 5:2058460116663046
34. Franiel T, Hamm B, Hricak H. Dynamic contrast-enhanced magnetic resonance imaging and pharmacokinetic models in prostate cancer. *European radiology* 2011; 21:616-626
35. Rastinehad AR, Waingankar N, Turkbey B, et al. Comparison of Multiparametric MRI Scoring Systems and the Impact on Cancer Detection in Patients Undergoing MR US Fusion Guided Prostate Biopsies. *PLoS One* 2015; 10:e0143404. doi: 0143410.0141371/journal.pone.0143404. eCollection 0142015.
36. Zhao C, Gao G, Fang D, et al. The efficiency of multiparametric magnetic resonance imaging (mpMRI) using PI-RADS Version 2 in the diagnosis of clinically significant prostate cancer. *Clin Imaging* 2016; 40:885-888. doi: 810.1016/j.clinimag.2016.1004.1010. Epub 2016 Apr 1026.
37. Woo S, Suh CH, Kim SY, Cho JY, Kim SH, Moon MH. Head-to-Head Comparison Between Biparametric and Multiparametric MRI for the Diagnosis of Prostate Cancer: A Systematic Review and Meta-Analysis. *AJR Am J Roentgenol* 2018; 211:W226-W241. doi: 210.2214/AJR.2218.19880. Epub 12018 Sep 19821.
38. Alabousi M, Salameh JP, Gusenbauer K, et al. Biparametric vs multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naive patients: a diagnostic test accuracy systematic review and meta-analysis. *BJU international* 2019; 124:209-220
39. Liang Z, Hu R, Yang Y, et al. Is dynamic contrast enhancement still necessary in multiparametric magnetic resonance for diagnosis of prostate cancer: a systematic review and meta-analysis. *Transl Androl Urol* 2020; 9:553-573. doi: 510.21037/tau.22020.21002.21003.

40. Niu XK, Chen XH, Chen ZF, Chen L, Li J, Peng T. Diagnostic Performance of Biparametric MRI for Detection of Prostate Cancer: A Systematic Review and Meta-Analysis. *AJR American journal of roentgenology* 2018; 211:369-378
41. Kang Z, Min X, Weinreb J, Li Q, Feng Z, Wang L. Abbreviated Biparametric Versus Standard Multiparametric MRI for Diagnosis of Prostate Cancer: A Systematic Review and Meta-Analysis. *AJR American journal of roentgenology* 2019; 212:357-365
42. Greer MD, Shih JH, Lay N, et al. Validation of the Dominant Sequence Paradigm and Role of Dynamic Contrast-enhanced Imaging in PI-RADS Version 2. *Radiology* 2017; 285:859-869
43. Lu YF, Zhang Q, Yao WG, et al. Optimizing prostate cancer accumulating model: Combined PI-RADS v2 with prostate specific antigen and its derivative data. *Cancer Imaging* 2019; 19:26
44. Vos EK, Litjens GJ, Kobus T, et al. Assessment of Prostate Cancer Aggressiveness Using Dynamic Contrast-enhanced Magnetic Resonance Imaging at 3 T. *European urology* 2013;
45. Giganti F, Allen C, Emberton M, Moore CM, Kasivisvanathan V, group Ps. Prostate Imaging Quality (PI-QUAL): A New Quality Control Scoring System for Multiparametric Magnetic Resonance Imaging of the Prostate from the PRECISION trial. *Eur Urol Oncol* 2020;
46. Engels RRM, Israel B, Padhani AR, Barentsz JO. Multiparametric Magnetic Resonance Imaging for the Detection of Clinically Significant Prostate Cancer: What Urologists Need to Know. Part 1: Acquisition. *European urology* 2020; 77:457-468
47. Sackett J, Shih JH, Reese SE, et al. Quality of Prostate MRI: Is the PI-RADS Standard Sufficient? *Academic radiology* 2020;
48. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. In. Arnhem, The Netherlands, 2020
49. Wirth M, Fossati N, Albers P, et al. The European Prostate Cancer Centres of Excellence: A Novel Proposal from the European Association of Urology Prostate Cancer Centre Consensus Meeting. *European urology* 2019; 76:179-186
50. Eldred-Evans D, .., Ahmed H. PROSTAGRAM study: MRI Screening May Help Diagnose Clinically Significant Prostate Cancer Better Than PSA Alone. *JAMA oncology* 2020;
51. Boesen L, Norgaard N, Logager V, et al. Prebiopsy Biparametric Magnetic Resonance Imaging Combined with Prostate-specific Antigen Density in Detecting and Ruling out Gleason 7-10 Prostate Cancer in Biopsy-naive Men. *Eur Urol Oncol* 2019; 2:311-319
52. Knaapila J, Jambor I, Perez IM, et al. Prebiopsy IMPROD Biparametric Magnetic Resonance Imaging Combined with Prostate-Specific Antigen Density in the Diagnosis of Prostate Cancer: An External Validation Study. *Eur Urol Oncol* 2019;
53. Padhani A, Barentsz J, Weinreb J, Schoots I, Tempany C. Lessons learned for the prostate cancer MRI-directed diagnostic pathway from the Positive Predictive Value: the need for end-to-end quality *European urology* 2020;
54. Sonn GA, Fan RE, Ghanouni P, et al. Prostate Magnetic Resonance Imaging Interpretation Varies Substantially Across Radiologists. *Eur Urol Focus* 2017;

55. Westphalen AC, McCulloch CE, Anaokar JM, et al. Variability of the Positive Predictive Value of PI-RADS for Prostate MRI across 26 Centers: Experience of the Society of Abdominal Radiology Prostate Cancer Disease-focused Panel. *Radiology* 2020:190646
56. Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists. *Radiology* 2016; 280:793-804
57. Park KJ, Choi SH, Lee JS, Kim JK, Kim MH. Inter-reader Agreement in Prostate Imaging Reporting and Data System Version 2 for Prostate Cancer: A Systematic Review and Meta-Analysis. *The Journal of urology* 2020:101097JU0000000000001200
58. Elkhoury FF, Felker ER, Kwan L, et al. Comparison of Targeted vs Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. *JAMA Surg* 2019;
59. Padhani AR, Barentsz J, Villeirs G, et al. PI-RADS Steering Committee: The PI-RADS Multiparametric MRI and MRI-directed Biopsy Pathway. *Radiology* 2019:182946
60. Force USPST, Grossman DC, Curry SJ, et al. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA : the journal of the American Medical Association* 2018; 319:1901-1913
61. Morote J, Celma A, Roche S, et al. Who Benefits from Multiparametric Magnetic Resonance Imaging After Suspicion of Prostate Cancer? *Eur Urol Oncol* 2018;

Table 1. Balancing the impacts of omitting contrast medium in MRI-directed prostate cancer diagnosis

Impacts on	Positive impacts	Negative impacts
Operations *(section 2.1)*	• Shortened examination times • Increased patient throughput • Reduced contrast-medium related operational issues - less pre-MRI patient paperwork, documentation, patient questionnaires, pre-MRI blood workup and safety checks (e.g., renal function assessments, allergies) - no concerns regarding potential contrast-related side-effects - no prevention actions to potential contrast-related side-effects (e.g. antihistamines, steroids) - no contrast-related infrastructure (e.g. inserting and removing cannulas, preparing injector apparatus, gadolinium-based contrast medium, staff) - no post-MRI concerns regarding contrast-related side-effects • Reduced need for 'in-room' monitoring and 'in-house' presence of medical back-up	• (none)
	Notes: impacts on reading times of examinations is not known	
Patient preference *(section 2.1)*	• Reduced patient discomfort - shorter on-table magnet time - no discomfort from i.v. cannula placement • No potential for contrast media related side-effects	• Potential for delayed diagnoses

	- hematoma, contrast extravasation, rare allergic reactions, potential for nephrogenic systemic fibrosis in patients with impaired renal function, potential for intracranial gadolinium deposition	
	Notes: For patients the best diagnostic test is preferred	
Image assessments *(section 2.2)*	• No impact on reading judgments in MRI negative cases (can be identified by using T2W and DWI criteria alone) • No impact on reading judgments in MRI positive cases, i.e. larger tumors, assigned as PI-RADS 5 and a substantial proportion of PI-RADS 4 lesions • No major impact on clinical decisions regarding the need for biopsies because in up to 80% of men, DCE-MRI has no effect on the final PI-RADS assignments	• Impact on the reading performance of less experienced readers • Impact on lesion PI-RADS assessments - increased proportion of indeterminate PI-RADS 3 cases, with greater uncertainty for readers and decision makers - unable to distinguish PI-RADS 3 cases from upgraded 3 to 4 (3+1) and from intrinsic PI-RADS 3 cases; all three distinct from intrinsic PI-RADS 4 cases may necessitate different biopsy plans • Impact on a key quality metric of prostate MRI which is to maintain low rates of PI-RADS 3 readings in biopsy naïve men • Impact on confidence and general adoption of non-contrast MRI approaches by healthcare systems and referrers • Patient recalls or on-table monitoring would be needed as a diagnostic safety-net, in case of indeterminate results or insufficient image quality
	Notes:	
Diagnostic performance *(section 2.3)*	• Potential to reduce contrast related false positive results and subsequent negative targeted biopsies	• Uncertainty in scientific strength of the non-contrast MRI observations in systematic analyses

	• Overall diagnostic test accuracies in meta-analyses show no statistical difference, when comparing non-contrast MRI and contrast MRI for all cancer detection - the proportion of negative non-contrast MRI is of similar magnitude to contrast MRI - the proportion of ISUP 2-5 or ISUP 3-5 cancers in negative non-contrast MRI are of similar magnitude to contrast MRI - in the minority of men with category 3 lesions on non-contrast MRI who are upgraded to PI-RADS 4 categories after DCE-MRI (3+1), the additional cancers detected are often ISUP=1 and microfocal ISUP=2 cancers	• Reviews on pooled data can only be considered being as broadly supportive of the non-inferior non-contrast MRI approach due to heterogeneity
	Notes: • Systematic reviews advise caution on taking non-contrast MRI test accuracies at face value data pointing to considerable heterogeneity amongst the included studies. - the definition of csPCa and the methods used for image evaluations vary widely. - in most studies, contrast MRI was used for deciding the need for biopsy and the choice of biopsy methods; that is, non-contrast MRI adoption conclusions are based on histologic verifications of contrast MRI decisions to biopsy. • There are few appropriately powered, prospective, multicenter, quality controlled studies comparing non-contrast /contrast MRI directed biopsies against systematic biopsies, measured for meaningful end-points related to clinical benefits (the correct diagnoses of csPCa, biopsy avoidance, precision in tumor grade or volume evaluations) and harms of testing (unnecessary testing, biopsy-related side-effects, over-diagnosis).	
Cost-savings *(section 2.1)*	• Increased operational / procedural efficacy • Decreased material / infrastructural use • Reduced prostate MRI related side-effects	• Potential for inferior performance - delaying diagnosis and treatment
	Notes:	
General comments *(section 2)*	• One of the major benefits of the MRI approach arises from biopsy avoidance resulting from negative MRI results, leading directly to reduce numbers of men undergoing invasive biopsy procedures, and to decreased rates of indolent cancer detection. Negative cases do not need dynamic contrast enhancement. • By necessity, any benefit of contrast medium administration (i.e. diagnostic performance) needs to be carefully balanced against actual and perceived potential harms	

	• The negative impacts of increased indeterminate cases and reader uncertainty may be mitigated by instituting patient recalls when needed, the so-called 'diagnostic safety-net' • The diagnostic safety-net use of DCE-MRI may well yield enhancing lesions that are imperceptible on T2W or DWI, but lesions revealed may not represent aggressive cancers that require immediate detection and treatment, with the potential to adversely impact on false positivity and targeted biopsy rates also. • Additional costs for contrast use also need to be justified in terms of the delivery of benefits in radiological assessments, diagnostic performance and clinical outcomes. • Potential for 'deep-learning' based artificial intelligence or computer-aided detection diagnostic support tools for image analysis	

Table 2: head-to-head studies comparing non-contrast and contrast MRI on reader performance and cancer detection rates

Author (year)[ref#]	Popualtion	MRI scoring (positive = bx)	Reference test	Defintion csPCa	Included patients		non-contrast MRI						contrast MRI						Shift from contrast MRI to non-contrast MRI:					
							MRI				PCa		MRI				PCa		Δ positive MRI		Δ MRI-score 3		Δ any PCa		Δ csPCa	
							negative	positive			any PCa	csPCa	negative	positive			any PCa	csPCa						
							1-2	3-5	3	4-5			1-2	3-5	3	4-5			n	ratio	n	ratio	n	ratio	n	ratio
Data from diagnostic setting = reference to biopsies																										
El-Shater Bosaily (2020) [29]	bx naive	Likert (3-5)	TM bx	ISUP 2-5	497		121 (24)	376 (76)	158 (32)	218 (44)	n.a.	245 (49)	123 (25)	374 (75)	136 (27)	238 (48)	n.a.	245 (49)	-2	1.01	22	1.16	_	_	0	1.00
Zawaideh (2020) [24]	mixed	Likert (3-5)	T-bx, S-bx	ISUP 2-5	264		121 (46)	143 (54)	45 (17)	98 (37)	116 (44)	87 (33)	132 (50)	132 (50)	22 (8)	110 (42)	117 (44)	88 (33)	-11	1.08	23	2.05	1	0.99	1	0.99
Van der Leest (2019) [30]	bx naive	PI-RADS v2 (3-5)	T-bx, S-bx	ISUP 2-5	626		309 (49)	317 (51)	49 (8)	268 (43)	261 (42)	180 (29)	309 (49)	317 (51)	40 (6)	277 (44)	261 (42)	180 (29)	0	1.00	9	1.23	0	1.00	0	1.00
Junker (2019) [31]	n.a.	PI-RADS v2 (3-5)	T-bx, S-bx	ISUP 2-5	236		47 (20)	193 (82)	48 (20)	141 (60)	133 (56)	46 (19)	41 (17)	195 (83)	69 (29)	126 (53)	133 (56)	46 (19)	6	0.99	-21	0.70	0	1.00	0	1.00
Kuhl (2017) [32]	prior neg. bx	PI-RADS v2 (3-5)	T-bx	intermediate/high risk	542		343 (63)	199 (37)	n.a.	n.a.	154 (28)	138 (25)	343 (63)	199 (37)	n.a.	n.a.	156 (29)	139 (26)	0	1.00	_	_	2	0.99	1	0.99
Data from operative setting = reference to radical prostatectomy specimen																										
Choi (2019) [26]	n.a.	PI-RADS v2 (3-5)	T-bx, S-bx, RP	n.a.	113	R1	17 (15)	96 (85)	35 (31)	61 (54)	n.a.	74 (65)	17 (15)	96 (85)	13 (12)	83 (73)	n.a.	74 (65)	0	1.01	22	2.69	_	_	0	1.00
						R2	4 (4)	109 (96)	23 (20)	86 (76)	n.a.	83 (73)	4 (4)	109 (96)	10 (9)	99 (88)	n.a.	83 (73)	0	1.08	13	2.30	_	_	0	1.00
Thestrup (2016) [33]	n.a.	subjective score	T-bx, S-bx, RP	ISUP 2-5	204	R1	24 (12)	180 (88)	n.a.	n.a.	n.a.	64 (31)	5 (2)	199 (98)	n.a.	n.a.	n.a.	68 (33)	19	1.00	_	_	_	_	4	0.94
						R2	23 (11)	181 (89)	n.a.	n.a.	n.a.	65 (32)	27 (13)	177 (87)	n.a.	n.a.	n.a.	63 (31)	-4	0.99	_	_	_	_	-2	1.03
Franiel (2011) [34]	prior neg. bx	using published criteria	T-bx, S-bx, RP	n.a.	54		0 (0)	54 (100)	n.a.	n.a.	21 (39)	n.a.	0 (0)	54 (100)	n.a.	n.a.	21 (39)	n.a.	0	1.00	_	_	0	1.00	_	_

Table 2 (legend): from an in-depth analysis of studies included in systematic reviews and additional recent data, focusing only on direct head-to-head comparisons between non-contrast MRI and contrast MRI for cancer detection on a patient-level, revealed 5 diagnostic studies [24, 29-32] and 3 operative studies [26, 33, 34]. In the clinical diagnostic setting, non-contrast MRI enables equal detection of

any PCa (ratio 0.99-1.00) and csPCa (ratio range 0.99-1.00), because the threshold for biopsy (likelihood scores 3-5) are identical. However, non-contrast MRI leads to greater uncertainty in reading performance in the diagnostic setting with increases in the proportion of (1) overall positive assessments of MRI scans (ratio > 1.00) [24, 26, 29], and of (2) indeterminate score 3 cases (ratio > 1.00) [24, 29-31].

n.a.: not available; _: cannot be calculated; bx: biopsy; TM: template mapping; T: targeted; S: systematic; RP: radical prostatectomy; R: reader; PCa: prostate cancer; csPCa: clinically significant PCa; MRI: magnetic resonance imaging; n: number; Δ: delta, difference.

Table 3. Diagnostic metrics of non-contrast MRI and contrast MRI for detection of any prostate cancer and clinically significant prostate cancer, from published systematic reviews and meta-analyses.

Author (year)[ref#]	Characteristics of included studies					Results													
						Any prostate cancert (PCa)						Clinically significant prostate cancer (csPCa)							
						non-contrast MRI			contrast MRI			non-contrast MRI			contrast MRI			non-contrast MRI		contrast MRI	
	Study population	Studies on non-contrast and/or contrast MRI	Reference standard / Comparator test	Focus on either patient level or lesion level	Focus on either whole prostate or zonal location	n	sensitivity (95%CI)	specificity (95%CI)	n	sensitivity (95%CI)	specificity (95%CI)	n	sensitivity (95%CI)	specificity (95%CI)	n	sensitivity (95%CI)	specificity (95%CI)	n	CDR (95%CI)	n	CDR (95%CI)
No direct head-to-head comparison (non-contrast MRI vs contrast MRI)																					
Liang (2020) [39]	bx naive + prior bx neg + bx pos	non-contrast MRI *or* contrast MRI	prostatectomy or biopsy (systematic and/or targeted)	either patient or lesion level	either whole prostate or zonal location	40	0.77 (0.73-0.81)	0.81 (0.76-0.85)	8	0.84 (0.78-0.89)	0.82 (0.72-0.88)	12	0.78 (0.66-0.87)	0.77 (0.66-0.85)	22	0.81 (0.66-0.90)	0.70 (0.50-0.84)	–	–	–	–
Alabousi (2019) [38]	bx naive + prior bx neg + bx pos	non-contrast MRI *or* contrast MRI	prostatectomy or biopsy (systematic and/or targeted)	patient level	whole prostate	6	0.89 (0.79–0.94)	0.76 (0.54–0.89)	9	0.91 (0.86–0.95)	0.73 (0.56–0.85)	6	0.91 (0.79–0.96)	0.62 (0.34–0.84)	16	0.83 (0.74–0.89)	0.74 (0.62–0.83)	–	–	–	–
Niu (2018) [40]	bx naive + prior bx neg + bx pos	non-contrast MRI *or* contrast MRI	prostatectomy or biopsy (systematic and/or targeted)	either patient or lesion level	either whole prostate or zonal location	33	0.81 (0.76–0.85)	0.77 (0.69–0.84)	–	–	–	10	0.81 (0.69–0.89)	0.74 (0.54–0.80)	–	–	–	–	–	–	–
Drost (2019) [12]	bx naive + prior bx neg	non-contrast MRI *or* contrast MRI	systematic and targeted biopsy	patient level	whole prostate	–	–	–	–	–	–	–	–	–	–	–	–	6	1.03 (0.91-1.17)	16	1.18 (1.05 -1.33)
Direct head-to-head comparison (non-contrast MRI vs contrast MRI)																					
Alabousi (2019) [38]	bx naive + prior bx neg + bx pos	non-contrast MRI *and* contrast MRI	prostatectomy or biopsy (systematic and/or targeted)	patient level	whole prostate	–	–	–	–	–	–	6	0.91 (0.82-0.96)	0.73 (0.37-0.92)	6	0.92 (0.91–0.94)	0.65 (0.33–0.87)	–	–	–	–
Kang (2019) [41]	bx naive + prior bx neg	non-contrast MRI *and* contrast MRI	prostatectomy or biopsy (systematic and/or targeted) or clinical follow-up	either patient or lesion level	whole prostate	10	0.79 (0.69-0.87)	0.88 (0.73-0.95)	10	0.79 (0.69-0.87)	0.89 (0.70-0.96)	–	–	–	–	–	–	–	–	–	–
Niu (2018) [40]	bx naive + prior bx neg + bx pos	non-contrast MRI *and* contrast MRI	prostatectomy or biopsy (systematic and/or targeted)	either patient or lesion level	either whole prostate or zonal location	11	0.80 (0.71-0.90)	0.80 (0.64–0.96)	11	0.85* (0.78–0.93)	0.77 (0.58–0.95)	–	–	–	–	–	–	–	–	–	–
Woo (2018) [37]	bx naive	non-contrast MRI *and* contrast MRI	prostatectomy or biopsy (systematic and/or targeted)	either patient or lesion level	either whole prostate or zonal location	16	0.68 (0.62–0.75)	0.92 (0.90–0.95)	16	0.72 (0.66–0.79)	0.91 (0.88–0.94)	7	0.86 (0.76–0.96)	0.82 (0.75–0.89)	7	0.87 (0.78–0.97)	0.83 (0.76–0.89)	–	–	–	–

Table 3 (legend): Many studies include studies done before 2010, when examinations would not have met the PI-RADS standard. Differences in review designs account for differences between diagnostic performances; some reviews have included studies with either non-contrast MRI or contrast MRI results, others included only studies on head-to-head comparisons of non-contrast MRI and contrast MRI results. The mixing of populations (combining data obtained after the cancer diagnosis for treatment guidance with MRI data in the diagnostic work-up of patients) and the mixing of reference standards or comparator tests (i.e. radical prostatectomy specimens, template mapping saturation biopsies, systematic biopsies, or targeted biopsies only) for determining diagnostic metrics are serious hazards. Studies have also noted that the definition of csPCa and the methods used for image evaluations (e.g. clinical Likert and PI-RADS systems for both non-contrast and contrast MRI) vary widely between studies. Other sources of heterogeneity also significantly affect disease detection sensitivity including the type of coils used, magnetic field strength, use of ADC maps and ultra-high b-values, patient enrollment, and reader blinding. Because of the considerable heterogeneity amongst the studies evaluated, caution is advised on taking these pooled test accuracies at face value when recommendations are being made about the diagnostic use of non-contrast MRI for biopsy naïve men.

CI.: confidence intervals; _: cannot be calculated; bx: biopsy; PCa: prostate cancer; csPCa: clinically significant PCa; MRI: magnetic resonance imaging; n: number; Δ: delta, difference.

Table 4. Prerequisites for using non-contrast MRI in MRI-directed prostate cancer diagnosis

	Prerequisites	Key-findings and recommendations

1.	**High quality imaging** *(section 3.1)*	• any negative impact resulting from insufficient quality will have adverse, compounding consequences on the whole of the MRI-directed diagnostic pathway
		• optimal image-acquisitions are necessary on the premise that there is likely to be a degradation of non-contrast MRI test performance in clinical practice, compared to its use at ~~highly~~ expert centers
		• to obtain impeccable T2W/DWI quality, higher technical scanner standards for data acquisitions need mandating by using
		  ○ optimized coil sets, with appropriate acquisition matrices, field-of-views, TR/TE and receiver bandwidth settings
		  ○ optimized b-values for ADC mapping and artifact-free high b-value DWI
		  ○ dedicated MRI radiographers/technologists/physicists, with continuous monitoring for quality
		• image quality should be assessed as part of routine non-contrast MRI reporting, with statements indicating whether the image quality is sufficient for 'ruling-in' and 'ruling-out' csPCa
		• an auditable, end-to-end quality approach is advisable in the entire non-contrast MRI-directed diagnostic chain (from patient-selection to non-contrast MRI to biopsy-results)
		• greater engagement by MRI machine manufacturers, willing and able to meet the requirements for non-contrast MRI use

2.	**High reader expertise** *(section 3.2)*	• the absence of contrast medium has an impact on the reading performance of less experienced readers in all zones of the prostate gland
		• high reader expertise in non-contrast MRI will positively impact on
		  ○ the diagnostic performance of MRI
		  ○ the confidence and adoption by urologists
		  ○ the ability to influence biopsy decisions
		• centers utilizing non-contrast MRI may consider concentrating the MRI-directed diagnostic work-up around dedicated radiologists and urologists, participating in multidisciplinary team meetings
		• accurate detection and characterization of suspicious foci of csPCa requires knowledge of age related gland anatomy, of benign findings, pitfalls and prostate cancer's natural structure and behavior, and how these relate to the observed radiological MRI phenotype

3.	**Adjustments of biopsy decision thresholds**	• in low disease prevalence settings, a non-contrast MRI approach with a PI-RADS 4-5 cut-off seems justified to minimize over-diagnosis achieving a better balance between sensitivity and specificity with fewer false positive cases

	according to clinical risks *(section 3.3)*	• in higher disease prevalence settings, a non-contrast MRI approach with a PI-RADS 3-5 cut-off for biopsy, is the default and likely to be the same as when using contrast MRI • adjustments of non-contrast MRI biopsy thresholds will have impacts on reader performance and on the diagnostic performance of MRI, and will require redocumentation for benchmarking purposes
4.	**Reader performance assessments and benchmarking** *(section 3.4)*	• in non-contrast MRI, there is a more pressing need for peer review, at least informally ○ within multidisciplinary meetings, where consistency and discrepancy between non-contrast MRI, biopsy and histological outcomes can be monitored ○ between readers and/or centers, with checking of inter- and intra-observer variability
5.	**Diagnostic safety-net: patient recalls or on-table monitoring** *(section 3.5)*	• instituting patient recalls will become necessary in non-contrast MRI, as part of the delayed 'diagnostic safety-net' use of DCE-MRI: ○ when there is insufficient quality of T2W or DWI images ○ in indeterminate cases ○ disadvantages: delays in diagnosis, patients lost to follow-up, and loss of urologic confidence in the technique • direct monitoring when the patient is on the scanner could minimize patient recalls ○ disadvantages: logistically challenging (trained radiographers/technologists), probably not cost-efficient from a scheduling perspective.
6.	**Monitoring safety-net** *(section 3.6)*	• in men avoiding immediate biopsies after a negative scan result, the 'monitoring or follow-up safety-net' after low likelihood non-contrast MRI findings in intermediate and high-risk biopsy-naïve men should be undertaken: ○ clinical examination and laboratory assays repeated imaging with DCE-MRI as per local clinical practice and consistent with clinical goals for individual patients

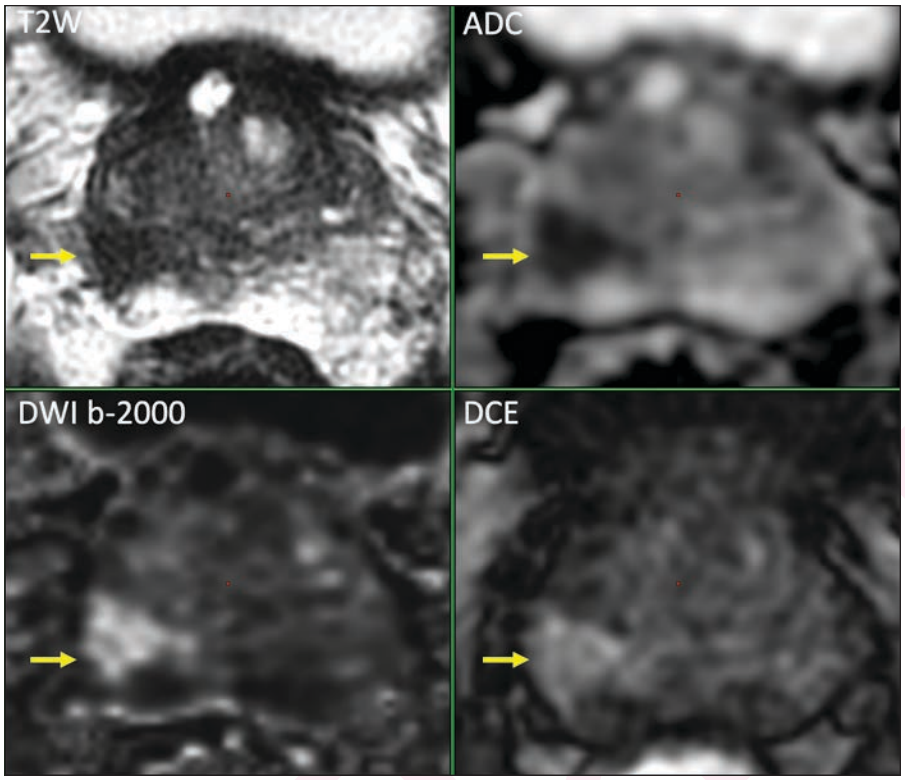

Figure 1. DCE-MRI does not add value in larger lesions with PI-RADS 4 or 5 scores in non-contrast MRI. 72 year-old man, cT1, PSA 8.1 ng/ml, PVmri 36 ml, PSAD 0.23 ng/ml2, primary diagnosis. Suspected lesion of 16 mm right peripheral zone with PI-RADS score 5 (T2W:5, DWI/ADC:5, DCE:+). DCE did not add value in this large PI-RADS 5 lesion. Three MRI-directed fusion biopsies revealed Gleason score 3+4=7 (ISUP grade 2) without cribriform / intraductal growth.

cT: clinical T-stage; PSA: prostate specific antigen; PVmri: MRI prostate volume; PSAD: PSA-density; T2W: T2 weighted imaging; DWI: diffusion weighted imaging; b: b-value of DWI; DCE: dynamic contrast enhanced imaging.

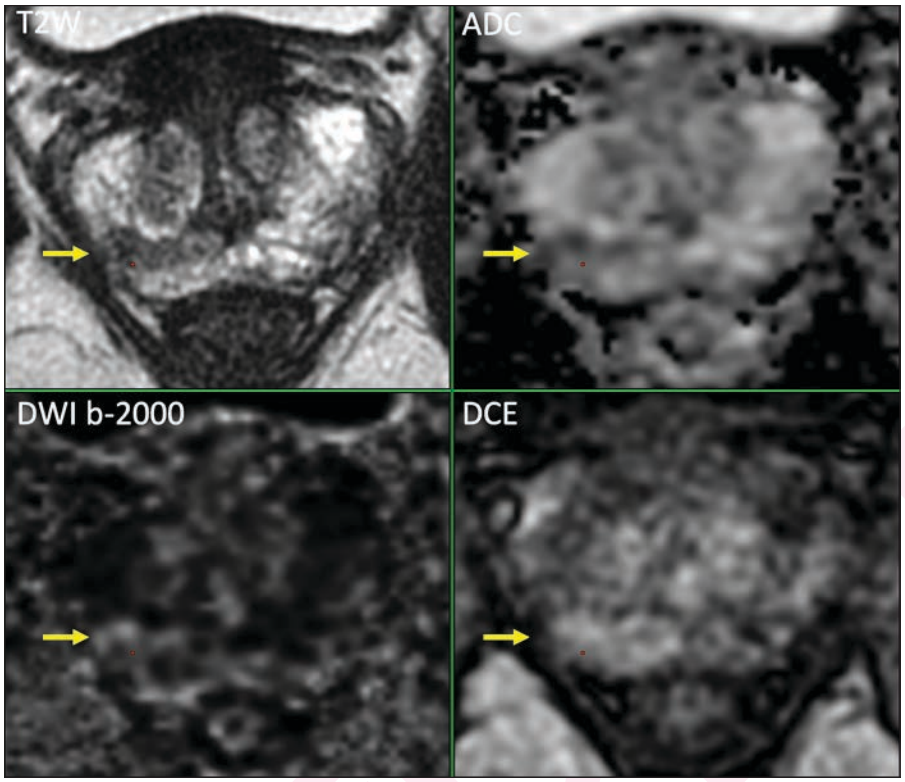

Figure 2. DCE-MRI adds value in indeterminate lesions with PI-RADS 3 scores in non-contrast MRI. 65 year-old man, cT1, PSA 3.5 ng/ml, PVmri 45 ml, PSAD 0.08 ng/ml2, primary diagnosis. Suspected lesion of 6 mm right peripheral zone with PI-RADS score 4 (upgraded 3+1) (T2W:3, DWI/ADC:3, DCE:+). This wedge-shaped lesion on T2W showed hardly any suspicious diffusion restriction on b-2000 (equivocal score 3), and a small focus with moderately decreased signal intensity on ADC. DCE showed a larger region of focal enhancement (+), and supported the equivocal score 3 of DWI/ADC, upgrading to a final PI-RADS score 4, indicating targeted biopsy. Three MRI-directed fusion biopsies revealed Gleason score 3+3=6 (ISUP grade 1) without cribriform / intraductal growth, in all three biopsies.

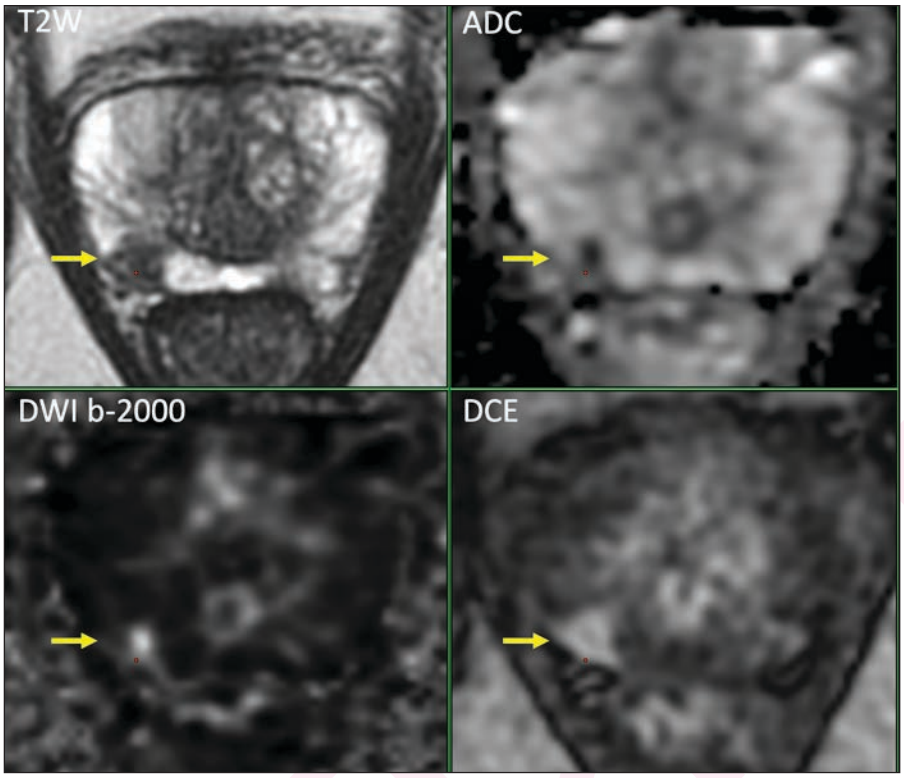

Figure 3. DCE-MRI adds value in smaller lesions with PI-RADS 4 scores in non-contrast MRI. 68 year-old man, cT1, PSA 8.6 ng/ml, PVmri 34 ml, PSAD 0.25 ng/ml2, primary diagnosis. Suspected lesion of 6 mm right peripheral zone with PI-RADS score 4 (T2W:4, DWI/ADC:4, DCE:+). This wedge-shaped lesion on T2W showed microfocal marked diffusion restriction b-2000 and ADC. Despite wedge-shaped characteristics, as a benign feature, lesional focal enhancement (DCE+) supported the DWI/ADC suspicion, and increased reader confidence. Five MRI-directed fusion biopsies (including penumbra) revealed Gleason score 3+4=7 (ISUP grade 2) with cribriform / intraductal growth (reduced prognostic prostate cancer), in all three biopsies.

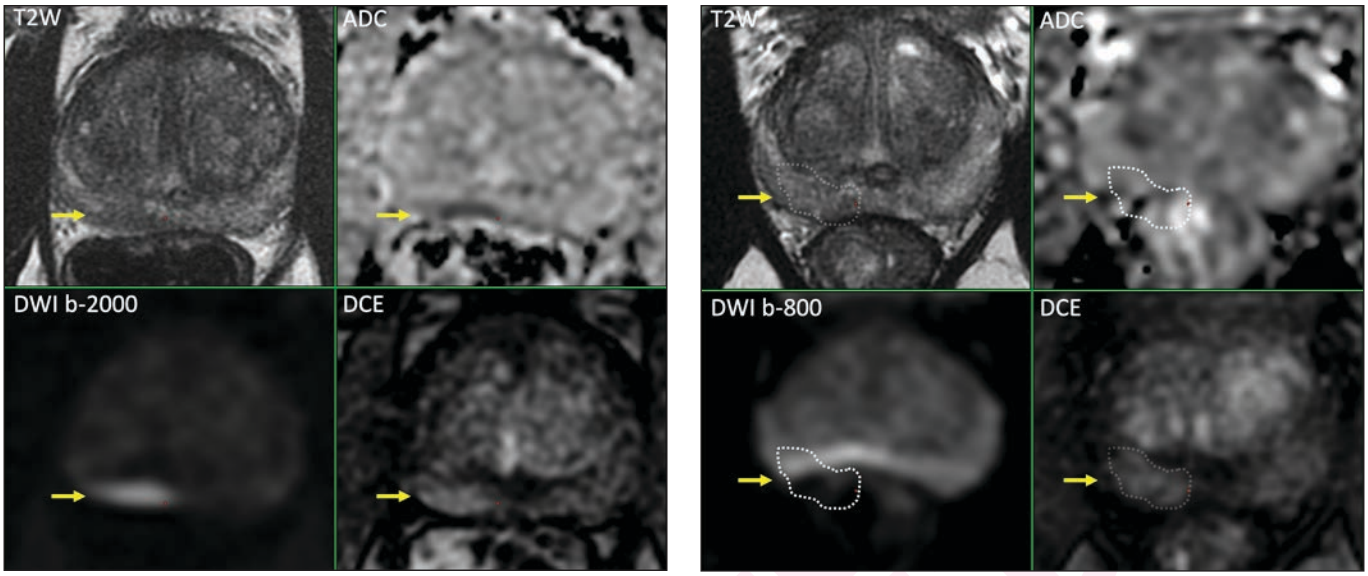

Figure 4. DCE-MRI adds value in non-contrast MRI with insufficient quality. 73 year-old man, cT1, PSA 9.4 ng/ml, PVmri 56 ml, PSAD 0.18 ng/ml2, primary diagnosis. (a) In the right peripheral zone a lesion of 12 mm showed little focal enhancement on DCE, however, not discriminative on T2W, as a result of diffuse low signal of the whole peripheral zone. Owing to air in the rectum, DWI/ADC show artefacts, disrupting the K-space of the peripheral zone. DWI/ADC were not diagnostic for the peripheral zone. (b) Following patient recall, MRI showed a thin subcapsular 12 mm lesion in the right peripheral zone, best identifiable on b-2000/ADC, with focal enhancement. Final score was PI-RADS score 4 (T2W:3, DWI/ADC:4, DCE:+), indicating targeted biopsy. DCE of the first contrast MRI already indicated a suspected lesion in the right peripheral zone. Three MRI-directed fusion biopsies revealed Gleason score 3+4=7 (ISUP grade 2) without cribriform / intraductal growth, in all three biopsies.

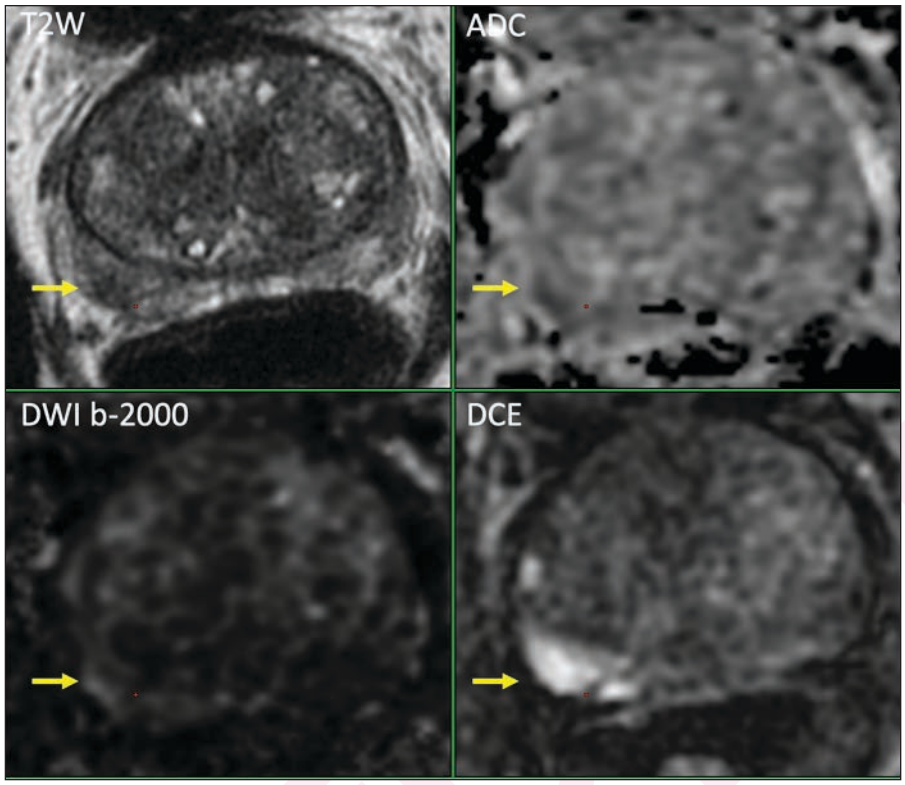

Figure 5. DCE-MRI adds value in some PI-RADS 2 scores in non-contrast MRI. 71 year-old man, cT1, PSA 8.2 ng/ml, PVmri 72 ml, PSAD 0.12 ng/ml2, primary diagnosis. In the right peripheral zone a lesion of 13-20 mm with heterogeneous but focal enhancement on DCE, barely identifiable on T2W or DWI/ADC. Final score was PI-RADS score 4 (upgraded 3+1) (T2W:3, DWI/ADC:3, DCE:+), indicating targeted biopsy. Without DCE this lesion would not have been identified. Two MRI-directed fusion biopsies revealed Gleason score 3+4=7 (ISUP grade 2) with cribriform / intraductal growth in both biopsies.

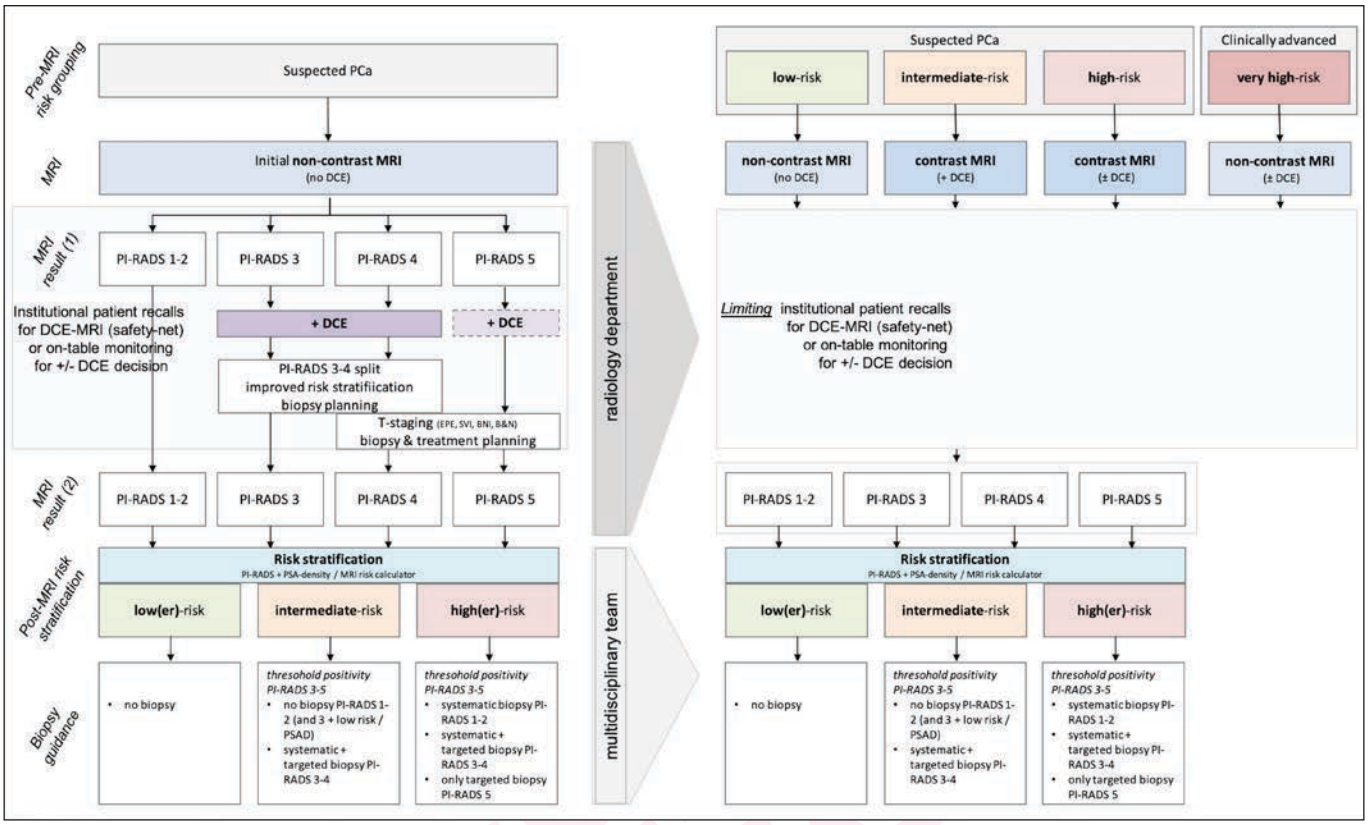

Figure 6. From a non-contrast MRI approach to a risk-based approach for non-contrast or contrast MRI decision, to simplify and improve efficiency of MRI-directed prostate cancer diagnosis.

a) (left) Suspected men of having clinically significant prostate cancer (csPCa) initially undergo non-contrast MRI, subsequently subcategorizing men into bpPI-RADS 1-5 groups. DCE-MRI is indicated in bpPI-RADS 3 and 4 cases, as it has potential additional value in the peripheral zone to improve the risk stratification of indeterminate lesions (PI-RADS 3) and for biopsy planning for smaller (PI-RADS 4) lesions. DCE-MRI could also be considered in some bpPI-RADS 5 cases, as part of improved T-staging (seminal vesicle invasion (SVI), neurovascular bundle (NVB) invasion, or bladder neck invasion (BNI)), and M1a-staging (bone and nodal (B&N) evaluations). On-table MRI monitoring would minimize the recall of patients with indeterminate results or with insufficient image quality of T2W and DWI (left), although this would be logistically challenging and difficult to realize in daily clinical working. Improved risk stratification based on mpPI-RADS scoring does not impact on biopsy decision for the majority, however, biopsy may be obviated in men with PI-RADS 3 scores with low PSA-density after multidisciplinary team (MDT) discussions.

b) (right) Pre-MRI risk assessments overcome the need for on-table MRI monitoring for contrast administration. Pre-MRI risk grouping of suspected men of having csPCa pre-sorts patients for non-contrast MRI (low-risk, and locally advanced disease) or to contrast MRI (intermediate- to high-risk men) examination strategies. Consequently, risk stratification of the PI-RADS categories 3 and 4 is preplanned, and staging is also enacted for higher clinical risk categories. DCE-MRI is omitted in the relatively large low-risk group, benefitting the operational diagnostic processes.

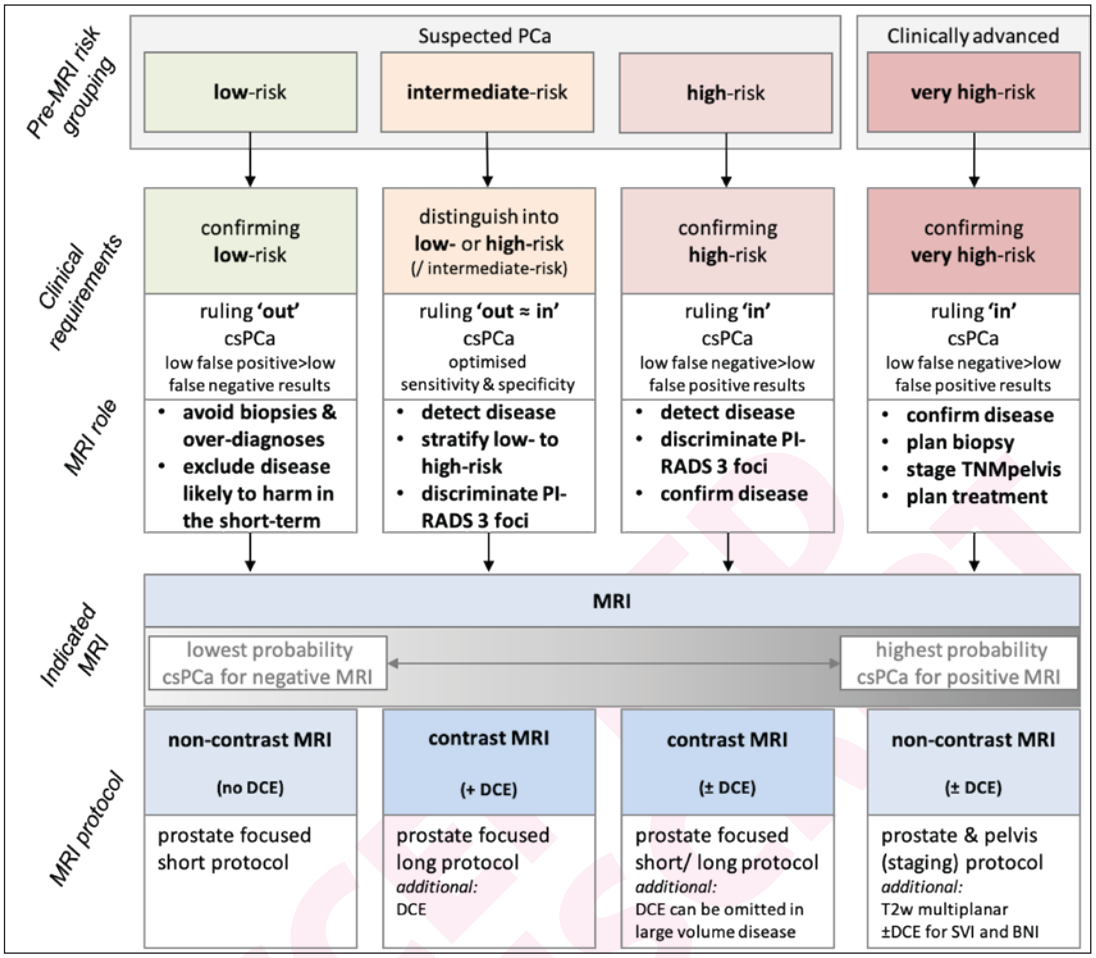

Figure 7. Risk-based approach for contrast MRI decisions for MRI-directed prostate cancer diagnosis.

Pre-MRI risk grouping of suspected men of having clinically significant prostate cancer (csPCa) into low-risk, intermediate-risk and high-risk, or even very high-risk (clinically advanced prostate cancer) allows the need for contrast MRI to be decided in advance.

In men at low-risk, MRI has a dual purpose: (1) to avoid over-diagnoses in the setting of a high background prevalence of ISUP=1 cancer in older men, and (2) to rule-out clinically significant disease with low false results because of the need to exclude disease that is likely to be harmfully in the short-intermediate term. This is a major clinical priority for biopsy naïve men. The balance between these competing clinical priorities is decided by the clinical priorities of men in shared decision making where MRI information can be helpful. A substantial proportion will most likely have a negative MRI. Non-contrast MRI (obviating DCE-MRI) may therefore be adequate in excluding disease (MRI-negative) and setting a high threshold for biopsy (PI-RADS 4-5) will balance over-diagnoses with under-diagnosis.

Men with intermediate- to high-risk should all undergo contrast MRI as a default. In high-risk men more than intermediate-risk men, MRI is performed to rule-in (i.e. to confirm) the presence and location of clinically significant disease. Dynamic contrast enhancement (DCE)-MRI has the potential for additional value to improve the risk stratification of indeterminate lesions (PI-RADS 3) and for biopsy planning for smaller (PI-RADS 4) lesions. Maximizing diagnostic yields and accurate histological assessments are clinical priorities in this group of men.

Men who are highly likely to have prostate cancer (very high-risk) based on very elevated serum PSA levels accompanied by abnormal digital rectal examinations, are unlikely to derive clinical benefits from DCE-MRI, and are better served with a non-contrast MRI done for local T-staging and to detect locoregional (pelvic) metastases. In these patients DCE-MRI may be omitted as large tumors are easily classified. There may be roles for contrast enhancement in selected patients for differential diagnosis or staging.

AJR

PI-RADS Committee Position on MRI Without Contrast Medium in Biopsy Naive Men with Suspected Prostate Cancer: A Narrative Review

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(footnote: Prostate Imaging Reporting and Data System)*

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