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Management of Patients With a Negative Multiparametric Prostate MRI Examination: AJR Expert Panel Narrative Review

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Abstract

Multiparametric prostate MRI (mpMRI) aids risk stratification of patients with elevated PSA levels. While most clinically significant prostate cancers are detected by mpMRI, insignificant cancers are less evident. Thus, multiple international prostate cancer guidelines now endorse routine use of prostate MRI as a secondary screening test before prostate biopsy. Nonetheless, management of patients with negative mpMRI results (defined as PI-RADS category 1 or 2) remains unclear. This AJR Expert Panel Narrative Review summarizes the available literature on patients with an elevated screening PSA level and a negative prostate mpMRI, and provides guidance for these patients' management. Systematic biopsy should not be routinely performed after a negative mpMRI in patients at average risk but should be considered in patients at high risk. In patients who undergo PSA screening rather than systematic biopsy after negative mpMRI, clear triggers should be established for when to perform a repeat MRI. Patients with negative MRI followed by negative biopsy should follow their healthcare practitioners' preferred guidelines concerning subsequent PSA screening for the patient's risk level. Insufficient high-level data exist to support routine use of adjunctive serum or urine biomarkers, artificial intelligence, or PSMA PET to determine the need for prostate biopsy after negative mpMRI.

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NT: none
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DM is an advisor for Promaxo
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MAG has served as a paid consultant and/or speaker for Ambu A/S; BK Medical ApS; Blue Earth Diagnostics; Corbin Clinical Resources, Inc. (Perineologic); Galvanize Therapeutics; KOELIS, Inc.; Lantheus Medical Imaging, Inc.; Merck & Co.; OBP Medical; POINT Biopharma; and Telix Pharmaceuticals

Introduction

Current guidelines from the American Urological Association, European Association of Urology, and NCCN recommend the routine use of multiparametric MRI (mpMRI) in patients with an elevated PSA level before such patients undergo a prostate biopsy [1–3]. This recommendation is based on a large body of level 1 evidence showing that limiting the performance of prostate biopsies to patients with a positive mpMRI leads to a reduction in the diagnosis of clinically insignificant prostate cancer (cisPCa) without compromising the detection of clinically significant prostate cancer (csPCa) [4–9]. Furthermore, the use of mpMRI has been shown to limit the number of false-negative biopsies by allowing MRI-directed targeted biopsies either alone or in combination with systematic sampling of the prostate [10].

Although patients with suspicious lesions detected on mpMRI should undergo a prostate biopsy, the management of patients with a negative mpMRI result remains unclear. In this *AJR* Expert Panel Narrative Review, we summarize the available literature on patients with an elevated screening PSA level and a negative prostate mpMRI, and provide guidance for the management of these patients. The presented principles are intended to apply for patients who are biopsy-naive, who have undergone a prior negative biopsy, or who are otherwise at average risk for developing prostate cancer (PCa), and do not apply for patients on active surveillance for known PCa. In addition, we recognize a burgeoning interest in performing prostate MRI without IV contrast medium (i.e., biparametric MRI), with ongoing prospective trials examining the technique's efficacy. However, this review exclusively addresses the use of MRI with contrast media (i.e., mpMRI), issuing guidance for management of patients with negative MRI on the assumption that mpMRI has been performed using minimum quality standards, and that the images are of diagnostic quality.

Standardized Performance and Reporting of Prostate mpMRI

PI-RADS was developed with the goal of expediting the dissemination of high-quality MRI to clinical settings, to improve the early diagnosis of clinically significant disease while reducing biopsies of benign tissue and subclinical disease [11]. PI-RADS achieves this goal by providing a standardized method for reporting findings on prostate MRI using a 5-point scale, corresponding with probabilities of csPCa [12], defined as PCa with International Society of Urologic Pathologists (ISUP) grade group (GG) ≥2 [13]. The latest version is PI-RADS version 2.1, which was released in 2019 [14]. PI-RADS version 2.1 introduced several changes to improve diagnostic performance and interobserver agreement while maintaining the system's overall scoring framework from the prior version [12,15,16]. When used appropriately, PI-RADS optimizes the likelihood of csPCa detection.

The detection rate for csPCa increases for increasing PI-RADS categories [13]. In a systematic review and meta-analysis from 2022, patient-level cancer detection rates for csPCa were 6% (95% CI, 0–20%) for PI-RADS category 1, 9% (95% CI, 5–13%) for PI-RADS category 2, 16% (95% CI, 7–27%) for PI-RADS category 3, 59% (95% CI, 39–78%) for PI-RADS category 4, and 85% (95% CI, 73–94%) for PI-RADS category 5

[17]. In that analysis, the overall yield of csPCa depended on the patient sample's disease prevalence, prior biopsy status, radiologist experience, and targeting biopsy accuracy [17]. A different meta-analysis of 56 studies found that biopsy-naive patients had a 10% higher yield for csPCa compared to patients with a prior negative biopsy (42% vs 32%, respectively) [18].

Salka et al. evaluated the effect of radiologists' prostate MRI interpretation experience on diagnostic performance [18]. For radiologists first 50 prostate MRI examinations interpreted, the PPV for Gleason sum score ≥7 was 51% (IQR, 42–60%) for PI-RADS category 4, compared to 70% (IQR, 54–75%) for PI-RADS category 5 [18]. For 101–150 examinations interpreted, the PPVs were comparable as for the first 50 examinations, but the IQRs did not overlap, suggesting that reader experience improved the interpretations' precision [19]. Another study observed moderate interreader agreement for PI-RADS categories at the whole-gland level (kappa = 0.65) [20].

MR image quality represents an additional important consideration. The Prostate Imaging Quality (PI-QUAL) system, released in 2020, can be used to rate the overall quality of the MRI examination [21]. In addition, the American College of Radiology (ACR) has implemented two major quality improvement initiatives to establish quality standards for prostate MRI examinations performed in the United States [22,23]. The first initiative was the establishment in 2022 of the Prostate Cancer MRI Center designation [22]. Eligibility for this designation requires that facilities meet minimum quality standards for MRI acquisition, technologist training, radiologist interpretation, radiology-pathology feedback, and access to MRI-guided fusion biopsy [22]. The second initiative is the ongoing ACR Learning Network [23]. In this initiative, enrolled sites, selected by an application process, seek to improve csPCa detection based on a collaborative continuous learning approach incorporating training and guidance from national experts in quality improvement strategies [23]. A prior *AJR* Expert Panel Narrative Review by Barrett et al. provides further discussion of quality standards for prostate MRI, including such issues as certification, experience-based outcomes, and quality control and assurance processes [24].

Definition of a Negative mpMRI

A negative mpMRI is most commonly defined as an mpMRI examination assessed as PI-RADS category 1 or 2 [25]. A total of 38% (95% CI: 36–40%) of patients who undergo mpMRI will have a negative mpMRI [26]. A meta-analysis of 42 studies found that the NPV of negative mpMRI in biopsy-naive patients was 90.8% (95% CI 88.1–93.1%), indicating that only approximately 9% of patients with PI-RADS category 1 or 2 have PCa with GG ≥ 2 [25]. In that study, the NPV of a negative MRI increased to 97.1% (95% CI 94.9–98.7%) for GG ≥ 3 [25]. A recent prospective, randomized controlled trial (the FUTURE trial) evaluated 431 patients with negative MRI and subsequent systematic biopsy for a median follow-up of 41 months; 13 (3%) patients were diagnosed with csPCa [27]. In that trial, significant predictive factors for csPCa were higher risk on a risk calculator and a suspicious result of repeat MRI [27]. The findings indicated that the vast majority of csPCa diagnostic in patients with a prior negative mpMRI are GG 2, and that 10 patients with negative MRI

would need to undergo a systematic biopsy to diagnose one patient with GG ≥2 disease. Figure 1 provides a graphical display of GG distributions for patients with negative mpMRI.

The diagnostic performance of PI-RADS categories 1, 2, 4, and 5 are well established, However, the diagnostic performance of PI-RADS category 3 is equivocal. Although PI-RADS category 3 lesions are typically considered to be positive and to warrant a targeted biopsy, some have suggested that, due to these lesions' indeterminate nature, they should be considered to represent a negative result in certain contexts [28–33]. PI-RADS category 3 lesions occur in approximately 20% of patients who undergo mpMRI [26]. Among PI-RADS category 3 lesions that are found to be cancer, most are GG 2 and thus have a low risk for progression [34]. For example, in one meta-analysis, PI-RADS category 3 lesions yielded PCa with GG 2 in 9.3% (95% CI 4.3–14.1), GG 3 in 1.5%, and GG 4 or 5 in 0.9% [35]. Factors such as smaller prostate volume, abnormal digital rectal examination, and high PSA density (PSAD) are associated with a higher likelihood of csPCa within PI-RADS category 3 lesions [36]. A PSAD cutoff of ≥0.15 ng/ml^2 has been found to be a significant predictor of csPCa; for example, in one study, a PSAD of 0.15–0.20 had a HR for csPCa of 3.23 (95% CI, 1.53–6.88)[36]. In comparison, a recent study suggested that a cutoff PSAD ≥0.20 ng/ml^2 may be preferable for risk stratification [37]. PSAD has been incorporated into nomograms for aiding the decision of whether to perform a prostate biopsy in patients with equivocal findings on mpMRI [38–40].

Harms of Prostate Biopsy

Except in rare instances, a prostate biopsy is required in order to render a diagnosis of PCa [40,41]. This procedure is typically performed using the transrectal approach under ultrasound guidance. Although generally well tolerated by patients, transrectal prostate biopsy is associated with infectious complications. According to a review published on behalf of the American Urological Association, 5–7% of transrectal prostate biopsy procedures are complicated by an infectious complication, with 1–3% of patients requiring hospitalization [42]. This risk has led to growing support for the transperineal approach to prostate biopsy, which has a nearly 10-fold lower risk of sepsis [43–45]. Nonetheless, transperineal prostate biopsy has not received widespread adoption globally and, instead, many urologists rely on culture-directed or augmented antibiotics to minimize the risk of infectious complications following transrectal biopsy [42].

Other biopsy complications include rectal bleeding, hematuria, urinary retention or bother, and transient erectile dysfunction [42]. An additional risk is the possible diagnosis of low-grade (i.e., GG 1) PCa (so-called "overdiagnosis"); the results of two large randomized clinical trials indicate that low-grade PCa does not require treatment and instead can be managed expectantly [46,47]. Overdiagnosis may be considered a risk of prostate biopsy given that a substantial proportion of patients diagnosed with low-grade PCa will opt for treatment by either radical prostatectomy or radiation therapy despite data on the safety of active surveillance. These treatments can lead to significant morbidity, including urinary, sexual, and bowel dysfunction [48–50]. More than 1 in 10 patients with localized PCa experience treatment-related regret [51]. Thus, limiting overdiagnosis and overtreatment can

be beneficial. Patients preferences to avoid prostate biopsy due to these issues must be recognized during biopsy decisions [52].

MRI-Invisible Tumors

Patients with MRI-invisible PCa often have lower PSA levels, larger prostate volumes, lower PSADs, and either clinically insignificant cancer (i.e., GG 1) or small-volume localized GG 2 disease [53–55]. In a post-hoc analysis of the patients cohort from the PROMIS trial, 13% of patients with negative mpMRI results (PI-RADS category 1 or 2) were found to have significant disease (all GG 2) [56]. Similarly, in a study by Lo et al. that included 73 patients with negative MRI after an earlier negative biopsy, no csPCa was diagnosed at follow-up in 70/73 (96.0%) patients, and only 4.0% (3/73) of patients were diagnosed with csPCa, which was GG 2 in all patients [57]. One study suggested that aggressive PCa variants, such as PCa with cribriform patterns, may be MRI-invisible [58]; however, subsequent larger studies reported that PCa with cribiform patterns are MRI-visible in >95% of cases [59], and that increasing PI-RADS categories correspond to increasing odds of the presence of cribriform patterns [60]. Buisset et al. reported a rate of csPCa of 6% on systematic biopsy performed after negative mpMRI [61]. In that study, 2% of patients who did not undergo treatment were diagnosed with PCa at a median follow-up of 4 years [61]; PSAD ≥0.15 ng/ml^2, clinical stage ≥T2a, and family history of PCa were predictors of csPCa. In a study of 1449 patients with csPCa on prostatectomy specimens, the cumulative incidence of metastatic disease was 0.61% for patients with MRI-invisible PCa, 3.5% for patients with MRI-equivocal PCa, and 19.6% for patients MRI-visible PCa, based on T2-weighted images on preoperative MRI [62]. The available literature overall indicates that patients with MRI-invisible PCa are expected to have a better prognosis than patients with MRI-visible PCa, with a low risk for progression, even if the PCa is not immediately detected; this view is supported by the 11-year risk of cancer death after a negative sextant prostate biopsy of approximately 0.2% [63]. The relatively good prognosis for patients with PCa and a negative MRI (i.e., MRI-invisible cancer) may in part reflect favorable genomics of MRI-invisible cancers, including a lack of genetic alterations that are associated with aggressive disease [64].

Management Pathways

In patients without known PCa, further management after a negative mpMRI depends on risk level. A negative mpMRI should not be routinely followed by systematic prostate biopsy in patients who are at average risk for developing PCa. However, systemic biopsy after negative mpMRI may be warranted in patients with clinical high-risk factors (e.g., elevated PSAD, identification as Black race, family history of PCa, or presence of genetic mutations known to increase the susceptibility to development of PCa). In patients who elect to undergo continued PSA screening rather than systematic biopsy after a negative mpMRI, clear triggers (e.g., based on PSAD or PSA velocity) should be established for when to perform a repeat MRI. Given insufficient data to guide this practice, the decision should be based on a model of shared decision-making between patients and their treating clinicians. Patients who choose to undergo biopsy after a negative mpMRI should be informed of the low likelihood of the biopsy yielding csPCa, as well as of the potential harms of PCa

treatment. Given the disparate PSA screening guidelines endorsed by organizations such as the NCCN [65], the U.S. Preventive Services Taskforce [66], and the American Urological Association [1], patients with negative MRI followed by negative biopsy should follow their healthcare practitioners' preferred guidelines concerning subsequent PSA screening for the patient's risk level.

Role of Adjunctive Testing

Ideally, patients with a negative mpMRI may be discharged from further PCa screening. However, as previously described, this approach is generally not recommended due to the suboptimal NPV of mpMRI for ruling out csPCa. Thus, other adjunctive tools have been explored, to employ in parallel to mpMRI, to bolster confidence in a negative mpMRI result. These adjunctive methods include serum and urine biomarkers, artificial intelligence (AI) tools, and PSMA PET.

Serum and Urine Biomarkers

Several serum- and urine-based biomarkers have been developed to aid risk stratification in patients presenting with an elevated PSA level. These tests include the 4Kscore, ExoDx, MyProstateScore (MPS), Prostate Health Index (phi), and SelectMDx, among others [67–69]. In general, these assays were developed before the widespread adoption of mpMRI and have not been validated in conjunction with mpMRI. Although some have advocated for the initial use of biomarker tests to aid in establishing which patients should undergo an mpMRI, high-quality data supporting this approach are lacking. Similarly, data supporting the use of these tests in the alternative scenario of selecting patient for a biopsy following a negative or equivocal mpMRI are limited to retrospective analyses. In one such analysis, Tosoian et al. found that the MPS test had utility in selecting which patients with a PI-RADS category 3 lesion were most likely to have a positive biopsy, outperforming clinical variables such as PSAD [28]. In another study, Calle et al. found that the use of the 4Kscore and/or ExoDx test following a negative mpMRI could reduce the false-negative rate on biopsy for detection of PCa with GG ≥2 to 2.4% [70]. Despite such findings, the authors of that study stated that they favored initial use of a biomarker to select which patients should undergo mpMRI, as a potentially more cost-effective approach. To our knowledge, the role of these biomarkers after a negative MRI has not been evaluated in prospective studies.

One biomarker test, ConfirmMDX, was developed specifically to identify patients who remain at risk for harboring PCa following a negative biopsy [71,72]. Thus, this test may also have a role in identifying patients with both a negative biopsy and negative MRI who remain at risk for PCa. Nonetheless, based on the low quality of the available data and the lack of cost-effectiveness analysis for these ancillary tests, we feel that, at present, there is insufficient evidence to endorse these biomarkers' routine use to aid in determining which patients with a negative mpMRI require a prostate biopsy.

Artificial Intelligence Tools

The high inter-reader variability of mpMRI may contribute to false-negative MRI results. The PRECISION trial reported a discordance rate between local interpretations and central

review of 22% for the differentiation of a PI-RADS category of 1 or 2 from a PI-RADS category of 3, 4, or 5 [4]. In contrast, the discordance for classifying a biopsy on histopathologic assessment as less than GG 2 versus greater than or equal to GG 2 was only 3% [4]. Similarly, Sonn et al. reported substantial variability in the distribution of PI-RADS categories and percent positivity for csPCa among nine radiologist at a tertiary care center [73]. Importantly, the frequency of false-negative findings on mpMRI ranged from 13–60% across readers. Given such data, treating clinicians have needed to remain vigilant following a negative mpMRI result, for concern of a missed csPCa.

AI tools for autonomous or supervised scan interpretation may help reduce the inter-reader variability in mpMRI interpretation. Although promising results have been described for several such AI tools [74–77], few have undergone external clinical validation, and even fewer have been incorporated into clinical-grade commercial products. This lack of integration in part relates to issues in the tools' generalizability for use with MRI examinations performed with different acquisition protocols or scanner equipment from those used to train the AI model. This issue was underscored in a recent systematic review, which reported that 18 of 35 (51.4%) AI tools for prostate MRI interpretation were trained or validated using scans from a single MRI manufacturer, and only 17 of 35 (20%) tools were developed using scans of differing magnetic field strengths [76]. Another concern with currently available AI tools relates to the underrepresentation of true-negative cases in most training datasets. This limitation stems from the fact that most patients with a negative mpMRI result do not undergo a prostate biopsy, which has classically served as the ground truth for model training. Both of these issues are being addressed by the ongoing Prostate Imaging: Cancer AI (PI-CAI) Challenge [78], a major international effort to integrate AI into clinical mpMRI interpretation based on a competition among AI researchers in the development of an AI tool for this purpose. The PI-CAI Challenge uses training data from multiple institutions that were acquired with a variety of MRI scanner protocols and technologies. Additionally, the challenge's dataset has been enriched to include negative mpMRI scans that use clinical follow-up to serve as the ground truth in place of histologic findings.

AI can also potentially improve the NPV of mpMRI by incorporating imaging parameters that are not recognized by PI-RADS. This concept is based on the hypothesis that the imaging data contain features that are not perceptible by human readers but that can improve the examination's intrinsic diagnostic yield. Discernment of such higher-order insights from the imaging data requires advanced AI tools such convolutional neural networks. Indeed, radiomic features extracted from MR images, such as peritumoral enhancement as well as other features not reflected in conventional human interpretations, have led to improvements in the accuracy of mpMRI [79–81]. The integration of such imaging features into mpMRI interpretation requires further study, although holds the potential to augment the confidence in a negative result.

PSMA PET

PET with radiotracers targeting the cell-surface protein PSMA has been shown to have better sensitivity and specificity for nodal and distant staging in patients with PCa compared

with CT, bone scan, and MRI [80–83]. As a result, PSMA PET is increasingly used for staging in patients with newly diagnosed unfavorable intermediate- or high-risk PCa, as well as for patients with a PSA elevation after definitive therapy for PCa. In both clinical scenarios, the primary goal of PSMA PET is to detect disease sites outside of the prostate. However, emerging data support a possible role for use of PSMA PET in combination with mpMRI for evaluating the prostate itself in patients with an elevated PSA level. The strongest data in support of this concept arise from the phase II PRIMARY trial, in which patients with an elevated PSA underwent both mpMRI and ^{68}Ga-PSMA-11 PET/CT before prostate biopsy [84]. In that trial, 56% of patients had csPCa on biopsy, of which 67% were positive on mpMRI, 73% were positive on PSMA PET, and 81% were positive on both modalities. Importantly, the NPV for csPCa improved from 72% for mpMRI alone to 91% for the combination of mpMRI and PSMA PET ($p < .001$). The PRIMARY II trial, a phase III, multi-center randomized controlled trial, is underway to evaluate whether PSMA PET is non-inferior to mpMRI for the detection of csPCa in patients with lesions classified as PI-RADS category 2 or 3 [85]. If positive, the PRIMARY II trial would provide further evidence supporting use of PSMA PET in patients with a negative mpMRI result, to provide the patient and treating clinician with additional confidence in the absence of csPCa. Nonetheless, the need for further follow-up in patients with both a negative mpMRI and a negative PSMA PET, as well as the intensity of any such follow-up, would still need to be determined.

Patient-Centered Care

Effective communication and patient education are core elements of shared decision-making, including in the context of PCa diagnosis and management. Clear and empathetic communication are critical in helping patients with a negative mpMRI to understand the implications of the test result. An understanding the specific risks, benefits, and uncertainties associated with a negative mpMRI result enables patients to make informed decisions that align with their individual preferences and values. Research supports that a collaborative approach involving the patient in decision-making leads to increased patient satisfaction and adherence to care plans [86]. A comprehensive educational and counseling process is thus fundamental in the management of patients with a negative prostate MRI, to lay a foundation for shared decision-making and patient-centered care.

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Consensus Statements

- These statements for the management of patients with negative mpMRI are intended to be applied for patients who are biopsy-naive, who have undergone a prior negative biopsy, or who are otherwise at average risk for developing PCa; the statements do not apply for patients on active surveillance for known PCa. In addition, the statements assume that patients have undergone mpMRI (not biparametric MRI), performed using minimum quality standards, and that the images are of diagnostic quality.
- When applying PI-RADS v2.1, a negative mpMRI (PI-RADS category 1 or 2) has a predictive value of approximately 90% for excluding clinically significant disease, defined as PCa with GG ≥2.
- Most patients with MRI-invisible PCa will be found to have insignificant PCa (i.e., GG 1) or small-volume localized GG 2 disease. A delay in diagnosis of MRI-invisible PCa with GG 2 does not appear to be associated with adverse patient outcomes.
- A negative mpMRI should not be routinely followed by systematic prostate biopsy in patients who are at average risk for developing PCa. Consideration of a systemic prostate biopsy after negative mpMRI may be warranted in patients with clinical high-risk factors (e.g., elevated PSAD, identification as Black race, family history of PCa, or presence of genetic mutations known to increase the susceptibility to development of PCa.
- Patients who opt to undergo a prostate biopsy after a negative mpMRI should be advised that the most likely biopsy outcome is the identification of clinically insignificant GG 1 PCa or small-volume localized GG 2 disease. The potential harms of PCa treatment should be communicated.
- Considering the disparate PSA screening guidelines endorsed by organizations such as the NCCN, U.S. Preventive Services Taskforce, and American Urological Association, patients with negative MRI followed by negative biopsy results should follow their healthcare practitioners' preferred guidelines concerning subsequent PSA screening for the patient's risk level.
- In patients who elect to undergo PSA screening rather than systematic biopsy after a negative mpMRI, clear triggers (e.g., PSAD or PSA velocity) should be established for wen to perform a repeat MRI. There are insufficient data to guide this practice, which should thus be based on a model of shared decision-making between patients and their treating clinicians.
- Insufficient high-level data exist to support the routine use of adjunctive serum or urine biomarkers to help determine the need for a prostate biopsy after a negative mpMRI.
- AI tools and PSMA PET may help in identifying patients with a false-negative mpMRI, but these adjunctive tests are not currently approved by

regulatory bodies for this purpose and thus cannot be recommended to guide management after a negative MRI.

- Effective patient communication, including education and counseling, is key for enabling patients to make informed decisions based on individual risk.

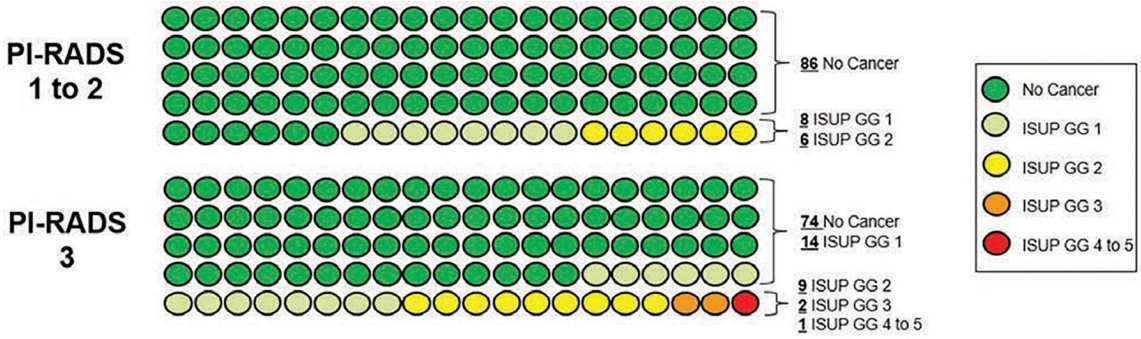

Figure 1.

Icon chart representing per-lesion diagnostic yield of PI-RADS category 1 and 2 compared to PI-RADS category 3, based on data in meta-analysis by Barkovich et al. [35]; values are rounded to nearest integer for purposes of graphic representation. As shown, risk of ISUP GG ≥ 3 in patients with PI-RADS category 1 or 2 is very low. International Society of Urological Pathology (ISUP); Grade Group (GG)