

American Urological Association (AUA) Society of Abdominal Radiology (SAR) Joint Consensus Statement

PROSTATE MRI AND MRI-TARGETED BIOPSY IN PATIENTS WITH PRIOR NEGATIVE BIOPSY

Collaborative Initiative of the American Urological Association and the Society of Abdominal Radiology's Prostate Cancer Disease-Focused Panel

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CONSENSUS STATEMENTS

- Following an initial negative biopsy, there is an ongoing need for strategies to improve patient selection for repeat biopsy as well as the diagnostic yield from repeat biopsies.
- Many options exist for men with a previously negative biopsy.
- If a biopsy is recommended, prostate MRI and subsequent MRI-targeted cores appear to facilitate the detection of CS disease over standardized repeat biopsy.
- Thus, when high-quality prostate MRI is available, it should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is undergoing a repeat biopsy.
- The decision whether to perform MRI in this setting must also take into account results of any other biomarkers, the cost of the examination, as well as availability of high quality prostate MRI interpretation.
- If MRI is done, it should be performed, interpreted, and reported in accordance with PI-RADS V2 guidelines. Experience by the reporting radiologist and biopsy operator are required to achieve optimal results and practices integrating prostate MRI into patient management are advised to implement quality assurance programs to monitor targeted biopsy results.
- Patients receiving a PI-RADS assessment category of 3-5 warrant repeat biopsy with image guided targeting.
- While TRUS-MRI fusion or in-bore MRI-targeting may be valuable for more reliable targeting, especially for MRI lesions that are small or in difficult locations, in the absence of such targeting technologies, cognitive (visual) targeting remains a reasonable approach in skilled hands.
- At least two targeted cores should be obtained from each MRI-defined target. Given a number of studies showing a proportion of missed CS cancers by MRI-targeted cores, a case-specific decision must be made whether to also perform concurrent systematic sampling.
- However, performing solely targeted biopsy should only should be considered

once quality assurance efforts have validated the performance of prostate MRI interpretations with results consistent with the published literature.

- In patients with a negative or low-suspicion MRI (PI-RADS assessment category of 1 or 2, respectively), other ancillary (i.e., PSA, PSAD, PSAV, PCA3, PHI, 4K) may be of value to identify patients warranting repeat systematic biopsy, although further data is needed on this topic.
- If a repeat biopsy is deferred on the basis of the MRI findings, then continued clinical and laboratory follow-up is advised and consideration should be given to incorporating repeat MRI in this diagnostic surveillance regimen.

INTRODUCTION

A majority of the prostate biopsies performed annually in biopsy-naïve men reveal no malignancy (1). However, many clinically significant cancers are missed (2). Thus, the subsequent management of patients with a prior negative biopsy and a persistently elevated or rising PSA represents a common and challenging clinical problem. Although general guidelines exist regarding the need for repeat biopsy, well-recognized consensus guidelines are lacking, and decisions are often driven by individual or local practice patterns.

The primary motivation for repeat biopsy is concern that a clinically significant cancer was missed on the initial biopsy. Often the serum PSA continues to rise after the negative biopsy, increasing the concern (3). Trans-perineal and trans-rectal extended saturation biopsy schemes can be used in this setting, yet these approaches entail increased risk of morbidity and may continue to miss significant cancers (2, 4, 5). The risk of cancer must be balanced against the cost, discomfort, anxiety, and potential complications of prostate biopsy, including hematuria, urinary retention, infection, and sepsis (6). A variety of biomarkers, including PSA derivatives such as the prostate health index (PHI) and 4K score, the urinary prostate cancer gene 3 (PCA3) test, and the epigenetic assay ConfirmMDx have been validated as methods to stratify the risk of cancer in such patients. The efforts to develop new biomarkers reflect the importance of improving patient selection for repeat biopsy. However, equally important to improved patient selection is improving the diagnostic yield of significant cancers at the time of repeat biopsy. While blood, urine and tissue based biomarkers may improve patient selection for repeat biopsy, such tests do not help to improve the diagnostic yield of the biopsy itself. In comparison, imaging has the potential to both improve patient selection and the yield of repeat biopsy.

Prostate MRI has undergone substantial technological improvement over the last ten years. Meanwhile, radiologists and urologists are gaining experience and training in prostate MRI, and uniform reporting standards are being established (7, 8). New technologies have been developed to facilitate the performance of biopsies targeting MRI-defined lesions

(9). As a result, an increasing number of urological practices are incorporating prostate MRI into the routine care of selected patients with a prior negative biopsy. Prostate MRI is increasingly used to identify patients warranting repeat biopsy by identifying regions of interest to target and to direct biopsies to these suspicious areas under image guidance. A growing body of literature demonstrates the value of MRI-targeted biopsy in the repeat biopsy setting. In this white paper, we evaluate the contemporary peer-reviewed literature on this subject as a basis for generating a summary consensus statement regarding the utilization of prostate MRI and MRI-targeted biopsy in patients with prior negative biopsy.

Current Guidelines

Current AUA guidelines provide indications for the performance of prostate biopsy solely for the initial biopsy setting(10). The National Comprehensive Cancer Network (NCCN) (version 2.2015) advises repeat biopsy after a negative biopsy if any of several criteria are met(11)(12): (1) initial biopsy demonstrating atypia or other findings suspicious for cancer, in which case an extended pattern re-biopsy is advised within six months, including increased sampling of the affected site and adjacent areas; (2) multifocal (>2 sites) of high-grade prostatic intraepithelial neoplasia (PIN), in which case a similar extended pattern re-biopsy within six months is advised; (3) focal high-grade PIN, in which case PSA and DRE are advised at a 1-year follow-up interval and consideration of repeat biopsy based on risk; and (4) benign initial biopsy not meeting any of the above criteria, in which case repeat biopsy is advised based on follow-up in 6-12 months using PSA/DRE or percent free PSA, 4K score, prostate health index (PHI), or PCA3. In the repeat biopsy setting, the NCCN guidelines advise that MRI with additional MRI-targeted cores be considered after at least one negative biopsy, although it does not explicitly recommend MRI be routinely performed.

The 2013 update of the European Association of Urology guidelines lists the following indications for repeat biopsy: rising and/or persistently elevated PSA, suspicious DRE, atypical small acinar proliferation, and multifocal high-grade PIN(12). The EAU guidelines indicate the optimal timing of the repeat biopsy is

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uncertain and if there is persistent clinical suspicion despite negative biopsies, then MRI with MRI-targeted cores may be performed to rule out an anteriorly located tumor.

Finally, the latest version of imaging recommendations for prostate cancer diagnosis and staging from the American College of Radiology from 2012 considered as "usually appropriate" the use of prostate MRI for men with prior negative biopsies when there was continued clinical suspicion for cancer(13).

Performance, Interpretation, and Reporting of Prostate MRI following a Negative Biopsy

The Prostate Imaging and Reporting Data System (PI-RADS) Version 2 (V2) was released in December 2014 (14)(15), representing the work of an international panel of leaders in the field of prostate MRI. PI-RADS is a comprehensive, publicly available online document that provides guidelines for the acquisition, interpretation, and reporting of prostate MRI. PI-RADS seeks to standardize the technique and interpretation of prostate MRI, reducing variability among readers and centers. The content of PI-RADS reflects the best evidence available at the time of its development, in combination with the expert opinion. It represents an expanded version of a more focused initial version (PI-RADS version 1) published in 2012(15). While PI-RADS provides guidelines for standardizing prostate MRI, performing consistent state-of-the-art prostate MRI remains challenging. Moreover, it is important for radiology practices performing prostate MRI to engage in continual quality improvement of their imaging and interpretation through adherence to standards and routine correlations of imaging results with histologic findings.

The guidelines provided by PI-RADS V2 for performing and interpreting prostate MRI are comprehensive and only briefly summarized here. PI-RADS V2 does not specifically require prostate MRI be performed either at 3T or using an endorectal coil, noting that clinically efficacious results can be obtained using a modern 1.5T system in combination with a multichannel receiver surface coil(14). Nonetheless, PI-RADS V2 states most of its authors favor use of a 3T system, when available, or use of an endorectal coil when using older-generation 3T or 1.5T systems. It is recommended to

delay MRI at least 6 weeks (if not longer), following biopsy to allow for resolution of post-biopsy hemorrhage, unless earlier diagnosis is deemed imperative. Measures are also encouraged to reduce the presence of feces and/or air in the rectum, which may cause distortion and other artifacts on the DWI portion of the MRI. These include using "minimal preparation" shortly before the MRI for phased-array coil exams, instructions for the patient to evacuate their bladder and bowels prior to the MRI, and use of a small suction catheter to decompress the rectum if initial images show excessive rectal air. In addition, it is considered diagnostically advantageous to have available at the time of MRI interpretation the patient's PSA history, prior biopsy results, and other relevant clinical history.

It is important that images be obtained in a standardized manner. PI-RADS V2 recommends prostate MRI protocols routinely include (1) multi-planar fast spin-echo or turbo spin-echo 2D T2-weighted imaging; (2) diffusion-weighted imaging (DWI) with a low b-value of 50-100 sec/mm², a high b-value of 800-1000 sec/mm², and possible additional intermediate b-values, in order to generate an apparent diffusion coefficient (ADC) map; and an additional "high" b-value image set using a b-value of at least 1,400 sec/mm² (which may be either directly acquired or calculated from the lower b-values); and dynamic contrast-enhanced (DCE) imaging using a rapid gradient-echo T1-weighted sequence (temporal resolution ≤ 15 seconds and optimally under 7 seconds; total observation time ≥ 2 minutes). MR spectroscopy is no longer considered a routinely acquired sequence. PI-RADS V2 recommends examination results be reported on a per-lesion basis, with lesion location defined on a 39-sector map. Each lesion's probability of representing clinically significant cancer is stratified on a 1-5 scale (referred to as the PI-RADS assessment category), with 5 indicating the highest likelihood, analogous to previously employed 1-5 Likert scales. Explicit criteria are provided for categorizing findings on T2WI as well as on DWI/ADC from 1-5 in both the peripheral zone and transition zone. Additional criteria are provided for deriving an overall 1-5 assessment category based on the individual sequence scores. The DWI/ADC score serves

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as the dominant score in deriving the overall assessment category in the PZ, and the T2WI score serves as the dominant score in deriving the overall assessment category in the TZ. PI-RADS simplifies the interpretation of DCE, classifying DCE findings as positive or negative based on a subjective visual evaluation, without requiring advanced software or post-processing to generate kinetic curves or colored pharmacokinetic maps. DCE findings influence the overall assessment category only for lesions that would otherwise be considered equivocal in the PZ based on DWI/ADC findings. An initial study of PI-RADS V2 demonstrated that the likelihood of diagnosing clinically significant (CS) cancers in both the peripheral and transition zones increased with increasing PI-RADS V2 score(16). An additional study indicated a kappa coefficient of 0.552 among experienced radiologists in the assignment of a PI-RADS V2 assessment category of at least 4, indicating moderate inter-observer agreement (17).

Quality Assurance of Prostate MRI Interpretation

A primary barrier to the widespread clinical adoption of prostate MRI has been marked variation not only in image quality, but also in radiologists' performance in exam interpretation. Prostate MRI image quality is influenced not only by the specific vendor and scanner model, but also by a wide array of acquisition parameters, such that exam quality may vary across centers employing the same MRI system based on the achieved level of scan optimization. Currently, there is no standardization for image quality. Moreover, interpretation of prostate MRI is inherently challenging as a result of a spectrum of diagnostic pitfalls that may result in either a false-positive or false-negative reading and thereby hinder performance. Indeed, the literature has demonstrated improved performance in prostate MRI interpretation among more experienced radiologists(18-20). For example, one study reported significantly greater diagnostic accuracy among radiologists with dedicated experience in prostate MRI than among radiologists with general expertise in body MRI(18). Thus, to date, implementation of prostate MRI and MRI-targeted biopsy has remained most heavily concentrated within major academic centers that have developed the necessary radiological experience and expertise to provide accurate MRI

interpretations. For prostate MRI to be widely adopted, community radiologists will also need to become trained and experienced.

As of this writing, there is no formal mechanism for radiologists to become certified in prostate MRI interpretation, nor an established number of examinations that must be interpreted in order for radiologists to achieve sufficient experience. However, various educational opportunities are available to assist radiologists in achieving the appropriate level of interpretive skill. Many hands-on courses and symposia are routinely offered that combine didactic lectures with interactive workshops and supervised case review at workstations(21), providing an opportunity for direct feedback from experienced radiologists serving as course guides. For example, one study demonstrated the ability to rapidly achieve significant improvements in radiologists' tumor detection, reader confidence, and prediction of significant cancer following a targeted educational program in prostate MRI(22). In addition, regular participation in a local multi-disciplinary conference attended by urologists, radiologists, and pathologists can facilitate dialogues among specialties that may improve the radiologist's reporting patterns. Perhaps most important, it is critical interpreting radiologists participate in ongoing case review, comparing prospective interpretations with subsequent histological results from targeted biopsy and prostatectomy. Such urological and pathological feedback is needed to help the radiologist identify and correct systematic causes of false-positive and false-negative interpretations. For example, Akin et al. demonstrated significant improvements in radiologists' interpretation when receiving individualized feedback comparing earlier interpretations with pathological tumor maps(23).

Given the challenges associated with prostate MRI interpretation, practices seeking to adopt a comprehensive program of diagnostic MRI and MRI-targeted prostate biopsy must actively engage in quality assurance efforts to ensure sufficient accuracy. Specifically, practices should seek to obtain histologic validation of their interpretations before broadly integrating prostate MRI into local practice. Since currently no quality standards or benchmarks for MRI interpretation or MRI-guided biopsies have been

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established, the authors of this white paper here propose benchmarks based on published reports from expert centers in combination with consensus experience and opinion. Two metrics considered most useful in assessing the accuracy of local prostate MRI interpretation are the cancer detection rate (CDR) at various PI-RADS thresholds as well as the miss-rate of MRI for clinically significant (CS) cancer. It is suggested that targeted biopsy of highly suspicious (PI-RADS 4) lesions yield GS \geq 3+4 tumor in \geq 30% of patients, and of very highly suspicious (PI-RADS 5) lesions yield GS \geq 3+4 tumor in \geq 70% of patients. In addition, it is suggested that MRI-targeted cores detect \geq 90% of GS \geq 3+4 tumors present on concurrently performed template biopsies, \geq 80% present on concurrent saturation biopsies, and \geq 70% present on excised whole prostates.

The consensus statements in the remainder of this white paper are contingent upon the availability of quality prostate MRI image acquisition and interpretations by individuals with sufficient experience and skill in the area, as well as of experience by the operators in performing the MRI-targeted biopsy. Provided sufficient expertise in prostate MRI interpretation and MRI-targeted biopsy, prostate MRI use can benefit the management of patients with a prior negative biopsy. Conversely, if expertise is lacking and the suggested benchmarks cannot be met, the clinical utility of prostate MRI proposed in this white paper is unlikely to be achieved and indeed misleading information and harmful consequences are possible. In this context, the authors of this paper strongly entreat radiologists interpreting MRI to pursue routine quality assessments, as well as education and other measures to improve the quality of their MRI interpretations.

Literature Review Goals and Methodology

We performed a review of the literature aimed at the following questions:

What is the impact of MRI following a negative prostate biopsy on the detection of CS cancer? Related to this, which patients should be offered prostate MRI following a negative biopsy?

Is there an optimal approach to performing repeat biopsies when a pre-biopsy MRI has been obtained?

Related to this, are advanced technologies for targeting suspicious regions on MRI required or recommended, and is there still a need to perform repeat standard systematic sampling at the time of repeat MRI targeted biopsy?

Can repeat biopsies be safely deferred based on a negative MRI? If so, what is the appropriate clinical follow-up in such patients and what is the role of non-imaging biomarkers in this context?

To answer these questions, we performed a search of PubMed for English-language articles using the following combination of key terms: "prostate," "biopsy," "negative" and either "MRI" or "magnetic resonance." Searches were conducted in September 2015. Each article was then evaluated for relevance and quality, in terms of reporting pathologic findings from biopsies performed in patients with at least one prior negative biopsy and who underwent MRI before the repeat biopsy. Articles were excluded if the MRI protocol did not include DWI or if it did not specifically discuss patients with a prior negative biopsy (i.e., biopsy naïve patients or patients on active surveillance) (24), if the previous negative biopsy was performed with MRI guidance, or if the repeat biopsy also was performed using contrast-enhanced ultrasound or ultrasound elastography. Included articles typically described the characteristics of patients, method for performing the targeting of MRI lesions, rates of detection of all cancer and of CS cancer on the post-MRI biopsy including the relative impact of MRI-targeted vs. systematic cores on CS cancer detection, association between MRI suspicion score (based on a variety of methods pre-dating PI-RADS V2) and ancillary laboratory biomarkers, and follow-up after a negative targeted biopsy or deferral of targeted biopsy. This white paper does not address the role of MRI in primary biopsy or in active surveillance.

RESULTS

Literature Results and Consensus Statement on the Detection of Clinically Significant Cancer at Repeat Biopsy using MRI Targeting

Numerous studies report the CDR of CS cancer on repeat biopsy using MRI targeting (Table 1). Variation likely represents differing criteria for CS cancer, patient

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selection for MRI and MRI-targeted biopsy, quality of the imaging, and the targeting methodology. The CDR of CS cancer on MRI-targeted biopsy in the re-biopsy setting ranges from 11-54%, although from 16-40% when restricting inclusion to studies that define CS cancer as having a Gleason score ≥ 7 (Table 1). Additionally, the data indicate the potential to increase CS cancer detection on repeat biopsy when comparing MRI-targeted biopsies to standard systematic sampling alone.

Literature results on patient selection for MRI after a negative biopsy

Obtaining an MRI following a negative biopsy generally indicates a persistent clinical suspicion for prostate cancer, most commonly based on a persistently elevated or rising PSA or abnormal DRE. The PSA cutoff to indicate persistent suspicion has varied across studies. A PSA threshold of 4.0 ng/mL has been most commonly used (28, 29, 31, 32, 34, 37-42), typically 4 to 10 ng/mL, and these generally indicate a utility for MRI before a repeat biopsy (43-45). The utility of MRI for lower PSA values has not been established. An elevated PSA velocity or rise in PSA above prior values has also been evaluated as an indication for MRI in the negative biopsy setting (27, 28, 35, 46).

Prior studies have also stratified the CDR of a repeat biopsy with MRI-targeting by the number of prior negative biopsies. When not incorporating pre-biopsy MRI or MRI-targeting, the cancer detection rate of repeat biopsy decreases with an increasing number of prior negative biopsies. For example, Roehl et al. reported a cancer detection rate of 17%, 14%, 11%, 9%, and 7% on the second through sixth biopsy (47), while Keetch et al. reported a cancer detection rate of 19%, 8%, and 7% on the second through fourth biopsy (3). However, when using pre-biopsy MRI, many studies have reported similar rates of detection of any cancer or of CS cancer, regardless of the number of prior negative biopsies (25, 28, 30, 33, 35, 36, 40, 46, 48, 49). For instance, Sonn et al. reported no change in significant cancer detection rate ($GS \geq 7$ or $CCL \geq 4$ mm) between patients with 1, 2, 3, or ≥ 4 negative biopsies (range, 23%-29%) (30).

Consensus statement on patient selection for repeat MRI directed biopsies

The accumulated evidence suggests prostate MRI has value for detecting CS cancer in patients with a prior negative biopsy and a persistently elevated or rising PSA, irrespective of the number of prior negative standard biopsies.

Literature results on the method of MRI-targeted biopsy

Three major strategies exist for targeting MRI-defined lesions in the repeat biopsy setting (9, 50-52). The approach involving the least amount of advanced technology is "cognitive" targeting, which involves estimating the location of a lesion detected on MRI and mentally transferring the target to the TRUS image during TRUS-guided biopsy without any technologic guidance. This approach does not require any additional hardware or software investment and can be applied in any clinical practice in which pre-biopsy MRI is available. The obvious limitation is the lack of visual feedback regarding accuracy of targeting the suspected cancerous lesion on MRI. Accuracy of this method is highly dependent on the operator's familiarity with prostate MRI and ability to accurately and consistently correlate MRI targets to real-time ultrasound images with reasonable fidelity. The reliability of this approach is of particular concern for lesions that are small, anterior, or in otherwise difficult-to-target locations. Nevertheless, good results with cognitive biopsy have appeared in the literature (44, 46, 53). In addition, cognitive targeting does not allow for spatial tracking of biopsy sites between biopsy sessions.

A second approach is to perform targeted biopsy while the patient is within the MRI gantry. With this technique, MR images can be obtained to confirm placement of the needle within the target. This approach offers the advantage of being the most direct targeting. However, the procedure is relatively time-consuming and labor-intensive, as well as potentially uncomfortable for the patient who is often in the prone position during the extended procedure time (45-60 minutes for multiple targets). In addition, concurrent systematic biopsies are not usually obtained because of time constraints of the in-bore procedure.

A third approach is real-time MRI/ultrasound fusion guided prostate biopsy. With this method, a planning session is performed in advance of the biopsy procedure in which the boundaries of the prostate and

Table 1-Literature summary regarding detection rate of clinically significant cancer on repeat biopsy using MRI targeting							
First author	Year	Study size	Type of MRI targeting	Definition of CS	SB CS+	TB CS+	Comments
Mendhiratta (25)	2015	210	Fusion	GS \geq 7	9%	16%	Among GS \geq 7 tumors, TB detected 90% and SB detected 52%
Arsov(26)	2015	104	Fusion	GS \geq 7	25%	26%	Data from "arm B" what is arm B?
Abdi(27)	2015	86	Cognitive (32) and fusion (54)	GS \geq 7, or >2 cores of >50% any core with cancer	24%	28%	29/30 CS tumors due to GS \geq 7. In 10% of patients, only TB + for CS tumor. CS tumor in 35% of patients undergoing SB+TB, compared with 16% of matched cohort undergoing only SB.
Salami(28)	2015	140	Fusion	Epstein's criteria	31%	48%	
Hambrock (29)	2010	68	In-bore	GS and either stage and volume in patients undergoing RP or PSA and PSA density in remaining patients		54%	\geq 2 prior negative biopsies
Sonn(30)	2014	105	Fusion	GS \geq 7 or GS6 with CCL \geq 4 mm	15%	21%	Not all patients underwent both SB and TB. 9 patients with CS cancer on TB were benign/insignificant on SB.
Kaufmann (31)	2015	35	In-bore	GS \geq 7	n/a	40%	GS in tumors detected by SB performed by separate operator not reported. However, 17% of patients had GS \geq 7 on TB and a benign SB.
Kaufman (32)	2015	49	In bore	Intermediate or high risk based on D'Amico criteria		39%	
Durmus(33)	2013	86	In bore	Intermediate or high risk based on D'Amico criteria		36%	
Hoeks(34)	2012	265	In bore	Combination of Epstein and d'Amico criteria		36%	
Roethke(35)	2011	100	In bore	GS and either stage and volume in patients undergoing RP or PSA and PSA density in remaining patients		42%	
Vourganti(36)	2012	195	Fusion	GS \geq 8	5%	11%	

the location of the target(s) are outlined on the MR images using vendor-specific segmentation software and needle tracking methods. The 3D prostate and target map are loaded into the fusion biopsy system before the biopsy. At the time of biopsy, the MRI data is fused to the TRUS imaging data using a combination of rigid and elastic registration to align the MRI and TRUS prostate segmentations. Once this is accomplished, movement of the TRUS is linked to a corresponding movement of the MRI so the biopsy can be performed under TRUS but using MRI guidance. This is achieved by either electromagnetic positioning devices on the TRUS probe, an articulated semi-automated robotic arm that tracks the motion of the ultrasound probe relative to the MRI, or a 3D ultrasound probe allowing real-time elastic registration with retrospective lesion targeting. Studies suggest reasonable registration accuracy of fusion algorithms with a registration error of approximately 3 mm(54-56). MRI-US fusion biopsy offers a number of advantages. Those who perform TRUS biopsy are already familiar with the principle elements of the procedure. The procedure duration is only ~5-10 minutes longer than routine TRUS biopsy, and can be incorporated into the existing clinical workflow. In addition, obtaining concurrent systematic cores, if desired, can be readily performed in the same session. Lastly, MRI-US fusion biopsy may enhance the collaboration between radiologists and urologists, taking advantage of their separate skill sets by allowing the radiologist to identify and annotate the location of MRI-defined targets while the urologist performs the actual biopsy. A potential disadvantage of this method is the possibility of co-registration error.

There are numerous studies showing utility for the detection of CS cancer using all three approaches: cognitive targeting(44, 46, 53), in-bore targeting (26, 27, 29, 31), and fusion targeting(24, 28, 30, 57, 58). However, there is a paucity of data directly comparing any two methods within the same cohort of patients having a prior negative biopsy. In one study, Wysock et al reported that among 34 patients with a prior negative biopsy, Gleason score ≥ 7 cancer was identified in 20.6% of patients by fusion biopsy, compared with 14.7% of patients by cognitive biopsy (non-significant difference, but underpowered study)

(45). Arsov et al. randomized patients with a prior negative biopsy to undergo either in-bore MRI-targeted biopsy or combined standard systematic and fusion-targeted biopsy. They identified no significant difference in the detection of any cancer or of CS cancer between the two groups(26). Finally, Puech et al. reported no significant difference in cancer detection or grading between cognitive and fusion targeted cores in the same patient sample, although their cohort combined biopsy-naïve and prior negative biopsy patients(59).

Consensus statement on the method of MRI directed biopsies

While use of advanced technology, such as a fusion system or in-bore biopsy system, may be helpful, the superiority of any specific approach has not been established. One approach may be to apply different methods of MRI targeting depending on characteristics of the lesion, for example using an in-bore or fusion system for lesions that are small or in a difficult-to-access region (i.e., the anterior or apical prostate), while limiting cognitive targeting to other lesions. While fusion and in-bore biopsy systems may have value in incrementally improving biopsy yield, they are expensive, and existing literature supports cognitive targeting as a sound approach for facilitating detection of CS cancer when advanced technologies are not available and operators are skilled with image guided procedures.

Additional considerations regarding conduct of MRI-targeted biopsy

During MRI-targeted biopsy, the large majority of studies report at least two cores from each MRI target (24, 26-29, 31, 32, 35, 36, 41, 43-45, 49, 53, 57, 60-63). Nonetheless, some studies report obtaining a larger number of cores (i.e, 4-6 cores) per lesion(24, 62). The number of cores may be increased for larger regions of interest (30, 49, 64). There is a paucity of data assessing the impact of a larger number of cores on cancer yield. Obtaining at least two cores from each target, with a larger number of cores at the discretion of the operator based on the lesion's size and location, as well as confidence in targeting accuracy, appears reasonable at this juncture.

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When performing MRI-targeted biopsy, approaches to pain control as well as the prevention and management of bleeding and infectious complications are similar to those for systematic biopsy(65). It is advised that systematic and MRI-targeted cores be separately labeled for purposes of pathologic analysis and reporting given that current accepted clinical nomograms are derived from data based on standard systematic biopsy results(66). In addition, the interpreting pathologist should routinely report the presence of inflammation, HGPIN, and ASAP within targeted cores, as the presence of a correlative histologic abnormality may provide assurance that the MRI-defined region-of-interest was accurately targeted when benign(45).

Literature results and consensus statement on the Need for Concurrent Systematic Sampling when Performing MRI Targeting

The high sensitivity of MRI-targeted cores for CS cancer raises the question of whether systematic cores are also warranted at the time of an MRI-targeted repeat biopsy(67). Numerous investigations indicate the presence of occasional CS cancers that are missed by targeted biopsy (Table 2). While the frequency is variable, the data suggests some CS cancers detected by systematic biopsies are missed by targeted biopsy (0-23%), even with optimized conditions and expertise. The quality of MRI acquisition and interpretation as well

as the targeting technique itself likely impact the detection of CS cancer. In addition, while the CDR of targeted biopsy for CS cancer is similar regardless of the number of prior negative biopsies, the likelihood of CS cancer being detected solely by systematic cores can be expected to depend on the number of prior negative systematic biopsy sessions. Nonetheless, some CS cancers falling below the threshold of MRI detection do exist. Thus, we advise that a case-specific decision must be made regarding whether to also perform concurrent systematic sampling at the time of targeted biopsy in order to maximize CS cancer detection. Deferral of concurrent systematic biopsy should only be considered when quality assurance has been performed to support the outcomes of MRI-targeted biopsy within the local practice.

Literature on Deferral of Repeat Biopsy Based on MRI Findings

MRI performed before a repeat biopsy may be used for more than simply identifying biopsy targets but also in providing the level of suspicion for clinically significant cancers on repeat biopsy. Numerous studies have reported outcomes of MRI-targeted biopsies in men with a prior negative biopsy stratified by the level of suspicion on MRI. While PI-RADS V2 employs a 5-point scale for stratifying level of suspicion, various other similar multi-point schemes have previously been used. Numerous studies have demonstrated suspicion scores

Table 2-Literature summary regarding clinically significant cancer missed by targeted biopsy

First author	Year	Study size	Targeting method	Criteria CS	MR-targeted biopsy miss rate for CS cancer
Abdi(27)	2015	86	Cognitive (32) and fusion (54)	GS \geq 7, or >2 cores of >50% any core with cancer	7%
Arsov(26)	2015	104	Fusion	GS \geq 7	18%
Tewes(68)	2015	39	Fusion	GS \geq 7	0%
Vourganti(36)	2012	195	Fusion	GS \geq 7	14%
Sonn(30)	2014	105	Fusion	GS \geq 7 or CCL \geq 4 mm	23%
Salami(28)	2015	140	Fusion	Epstein's criteria	4%

correlate strongly with the likelihood of CS cancer. For example, Kauffman et al. reported the presence of cancer on in-bore biopsy in all 155 patients with a PI-RADS score of 4, yet in 5 of 15 patients with a PI-RADS of 3(32); Meng et al. reported detection of GS \geq 7 tumor in 5-6% of patients with an MRI suspicion score of 2-3, 25% with a score of 4, and 83% with a score of 5(24); Portalez et al. reported a CDR of 3%, 11%, 38%, 63%, and 83% for MRI suspicion score of 1-5, respectively (58); Sonn et al. identified the MRI suspicion score to be the strongest predictor of CS cancer, with 86% of patients having PI-RADS 5 being found to have CS cancer(30), compared with only 2% from PI-RADS 2-3 lesions; and Salami et al. reported a CDR of 83% in patients with a PI-RADS of 4-5(28).

If a threshold MRI suspicion score can be identified that has sufficient sensitivity for CS cancer, then it may be possible that patients with a normal MRI, or an MRI suspicion score below this threshold, may not require a repeat targeted biopsy. Past studies have investigated

CDR in repeat systematic biopsies performed in the absence of suspicious lesions on MRI (Table 3), as well as the NPV of various PI-RADS categories with respect to concurrently performed systematic biopsy (Table 4). While suggesting a generally low frequency of missed cancer on MRI, such studies likely underestimate the true frequency of cancers missed on MRI given the lack of a reference standard such as radical prostatectomy, saturation or template biopsy, or long-term clinical follow-up.

Available evidence is inconclusive regarding outcomes when a repeat biopsy is deferred on the basis of MRI findings. Abdi et al. reported 24 patients with no suspicious lesion on MRI and in whom repeat biopsy was deferred and no patient had a change in PSA or DRE findings or was diagnosed with prostate cancer at a median follow-up of 16.7 months(27). In addition, Arsov et al. reported 30 patients in whom repeat biopsy was deferred after a normal MRI and none had a significant PSA increase or was diagnosed with cancer

Table 3- Literature summary regarding cancer detection rate in the setting of 'normal' MRI

Author	Year	Study size	CDR in neg MRI	Comment
Kuru	2013	347	15% any cancer	Trans-perineal
Pepe	2014	168	0% GS \geq 7	
Sciarra	2012	84	9% any tumor	
Girometti	2012	26	0% any cancer	

Table 4-Literature summary regarding the negative predictive value (NPV) of various PI-RADS categories with respect to concurrently performed systematic biopsy

First Author	Year	Study size	Targeting method	PI-RADS threshold	NPV based on systematic sampling	Comments
Portalez	2012	129	Fusion	3	95% for all cancer	
Tewes	2015	39	Fusion	4	92% for all cancer	
Mendhiratta	2015	172	Fusion	4	95% for GS \geq 7	
Abdi	2015	86	Cognitive (32) and fusion (54)	3	82.6% for CS cancer	CS defined as GS \geq 7, or >2 cores of >50% any core with cancer
Abd-Abd-Abd-Alazeez	2014	54	Cognitive	3	92% for GS \geq 7 and 100% for GS \geq 4+3	Trans-perineal template biopsy

at a median follow-up of approximately 1 year(37). Nonetheless, such studies are significantly limited given the inability to exclude significant cancer based on short-term PSA and clinical follow-up, and as noted, the literature suggests a rate of CS cancer on non-targeted biopsy in 0-23% of men with a negative MRI. Thus, a negative MRI cannot be viewed in clinical practice as an indicator of the absence of CS cancer, and if clinically indicated (e.g., persistent biomarker abnormality, strong family history, palpable lesion), a negative MRI should not at this time obviate a systematic biopsy.

Consensus statement on role of immediate re-biopsy after MRI

The available data suggest repeat biopsy in patients with persistent clinical suspicion for prostate cancer is justified in the setting of an MRI with a PI-RADS 4 or 5 lesion (a highly suspicious lesion) and that deferral of repeat biopsy may be considered in the setting of a negative (PI-RADS 1) or low-suspicion (PI-RADS 2) MRI in the absence of strong clinical suspicion. However, we believe there is insufficient data to support routinely deferring repeat biopsy of lesions receiving a PI-RADS assessment category of 3, for which CS cancer rates following targeted biopsy have been highly variable. Additionally, the available data indicates 5-15% of CS cancers remain undetected on MRI in the repeat biopsy setting. Therefore, CS cancer can never be entirely excluded on the basis of a negative MRI and continued clinical follow-up is warranted whenever repeat biopsy is deferred on the basis of a normal or low-suspicion MRI. While these considerations reflect the cumulative data of expert centers, application in individual practices warrants that practitioners assess the accuracy of MRI in their own hands to ensure the applicability of these summary statements.

Literature results on follow-up after negative MRI directed biopsies.

A number of studies have reported results from continued follow-up evaluation following a benign MRI-targeted biopsy in the repeat biopsy setting. Kauffman et al. reported no patient with a negative in-bore biopsy was diagnosed with prostate cancer after a median follow-up of 27 months (range, 23-60 months)(32). In a separate study, Kauffman et al. reported at median

33 months of follow-up (range, 18-53 months), no patient with a negative in-bore biopsy was diagnosed with prostate cancer(31). In contrast, a number of studies indicate CS cancer cannot be completely excluded based on a negative targeted biopsy. For example, Vourganti et al. reported that among 10 patients with a negative fusion biopsy who subsequently underwent an additional fusion biopsy, three were positive for cancer, one of which was high grade(36). In all three of these patients, the cancer was only identified on fusion cores, and none were originally low-suspicion MRI lesions(36). In addition, Kuru et al. reported that among 25 patients who underwent an additional biopsy at a median of 12 months following an initial negative targeted biopsy in the repeat biopsy setting, three were diagnosed with cancer, two of which had a primary Gleason pattern of 4(49). Moreover, Engehausen et al. reported that 10 of 57 patients with a negative in-bore biopsy were diagnosed with cancer within three years(69).

Consensus statement on follow-up after negative MRI directed biopsies.

Continued clinical follow-up and consideration of repeat biopsy remain warranted following a negative MRI-targeted biopsy. Such follow-up can be performed through a combination of serial PSA measurements, DRE evaluations, and possibly repeat MRI examinations. For an MRI lesion with very high suspicion (i.e., PI-RADS assessment category of 5) that is negative on targeted biopsy, an earlier repeat targeted biopsy should be considered(36).

Literature on the role of ancillary markers in MRI-targeted biopsies

A number of studies have evaluated whether ancillary laboratory data may be used in selecting whether MRI-based lesions warrant biopsy in the prior negative biopsy setting. For instance, Kauffman et al. reported PCA3 score was not helpful in predicting repeat biopsy results in the overall cohort, although it was helpful in patients with a PI-RADS score of 3(32). In this subset, all patients with a positive in-bore biopsy had a PCA3 score over 35, and in 6 of 10 patients with a negative biopsy, the PCA3 score was less than 35(32). When combining a threshold PI-RAD score of 3 and a

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threshold PCA3 score of 35, the measures achieved a NPV of 100% and PPV of 84.6%(32), however caution should be exercised when applying this data due to the small size of the study. Also, Hoeks et al. reported significantly more cancers were identified on in-bore biopsy in patients with a PSAD over, rather than below, 0.15 (52% vs. 24%, respectively)(34). Additional investigators have attempted to create multivariable models combining MRI findings and other laboratory data in predicting repeat biopsy results. MRI findings have consistently been retained as a significant independent factor in such models (Table 5).

Consensus statement on the role of ancillary markers in MRI-targeted biopsies

Non-imaging markers (i.e., PSA-based measures as well as PCA3) are likely useful in further selecting patients with a negative or low-suspicion MRI (PI-RADS score of 1 or 2, respectively) that may deserve a systematic biopsy despite the MRI results. However, targeted biopsy remains warranted for intermediate or high suspicion MRI lesions despite results from these ancillary markers given the consistently observed strong independent effect of the MRI suspicion score on

cancer detection in multivariate models. Further investigation is warranted to identify which of these markers best complements MRI findings in the repeat biopsy setting.

SUMMARY

Following an initial negative biopsy, there is an ongoing need for strategies to improve patient selection for repeat biopsy as well as the diagnostic yield from repeat biopsies. Many options exist for men with a previously negative biopsy. If a biopsy is recommended, prostate MRI and subsequent MRI-targeted cores appear to facilitate the detection of CS disease over standardized repeat biopsy. Thus, when high-quality prostate MRI is available, it should be strongly considered in any patient with a prior negative biopsy who has persistent clinical suspicion for prostate cancer and who is undergoing a repeat biopsy. The decision whether to perform MRI in this setting must also take into account results of any other biomarkers, the cost of the examination, as well as availability of high quality prostate MRI interpretation. If MRI is done, it should be performed, interpreted, and reported in accordance with PI-RADS V2 guidelines. Experience

Table 5- Literature results regarding key factors identified in multivariable analyses of MRI and laboratory biomarkers

Author	Year	Study size	Endpoint	Independent factors	Non-independent factors
Abdi	2015	86	GS \geq 7, or >2 cores of >50% any core with cancer	PI-RADS and PSAD >0.15 ng/ml ²	PSA, lesion size on MRI, number of prior biopsies, total # of cores, time interval, PSA velocity
Salami	2015	140	Epstein's criteria	MRI suspicion score	Age, ethnicity, family history, DRE, no. prior biopsies, PSA, PSAD, PSAV, prostate volume, lesion volume, lesion ADC, and EPE on MRI
Sonn	2014	105	GS \geq 7 or GS6 with CCL \geq 4 mm	PI-RADS, age, prostate volume, PSAD	Not identified
Vourganti	2012	195	GS \geq 7	MRI suspicion score and PSAD	Age, race, no prior biopsies, PSA, prostate volume
Porpiglia	2014	170	All cancer	"Base" model (DRE+age) and MRI (positive vs. negative)	PCA3, PHI
Busetto	2013	171	All cancer	"Base" model (age, PSA, DRE), MRI (positive vs. negative) and PCA3	

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by the reporting radiologist and biopsy operator are required to achieve optimal results and practices integrating prostate MRI into patient management are advised to implement quality assurance programs to monitor targeted biopsy results. Patients receiving a PI-RADS assessment category of 3-5 warrant repeat biopsy with image guided targeting. While TRUS-MRI fusion or in-bore MRI-targeting may be valuable for more reliable targeting, especially for MRI lesions that are small or in difficult locations, in the absence of such targeting technologies, cognitive (visual) targeting remains a reasonable approach in skilled hands. At least two targeted cores should be obtained from each MRI-defined target. Given a number of studies showing a proportion of missed CS cancers by MRI-targeted cores, a case-specific decision must be made whether to also perform concurrent systematic sampling. However, performing solely targeted biopsy should only be considered once quality assurance efforts have validated the performance of prostate MRI interpretations with results consistent with the published literature. In patients with a negative or low-suspicion MRI (PI-RADS assessment category of 1 or 2, respectively), other ancillary (i.e., PSA, PSAD, PSAV, PCA3, PHI, 4K) may be of value to identify patients warranting repeat systematic biopsy, although further data is needed on this topic. If a repeat biopsy is deferred on the basis of the MRI findings, then continued clinical and laboratory follow-up is advised and consideration should be given to incorporating repeat MRI in this diagnostic surveillance regimen.

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