

# Magnetic resonance imaging detection of prostate cancer in men with previous negative prostate biopsy

Matthew Truong, Thomas P. Frye

Department of Urology, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

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*Correspondence to:* Thomas P. Frye. Assistant Professor, University of Urology, Department of Urology, 601 Elmwood Ave, Box 656, Rochester, NY 14642, USA. Email: Thomas\_Frye@urmc.rochester.edu.

**Abstract:** Use of transrectal ultrasound guided systematic prostate biopsy has poor diagnostic accuracy for prostate cancer (PCa) detection. Recently multiparametric MRI (mpMRI) of the prostate and MR/US fusion biopsy has been gaining popularity for men who have previously undergone a negative biopsy. We performed PubMed® and Web of Science® searches to identify studies on this subject, particularly focusing on studies consisting of patients who have had at least one previously negative biopsy. Across the literature, when a suspicious lesion is found on mpMRI, MR/US fusion biopsy has consistently demonstrated higher detection rate for any PCa and clinically significant PCa (csPCa) compared to the traditional repeat systematic biopsy (SB) approach. Furthermore, anteriorly located tumors are frequently identified using MR targeted biopsy (TB), suggesting that an MR guided approach allows for increased accuracy for detecting tumors commonly missed by systematic biopsies. We conclude that men with a prior negative biopsy and continued suspicion of PCa should strongly be encouraged to get a prostate mpMRI prior to a repeat biopsy.

**Keywords:** Magnetic resonance imaging; prostate cancer (PCa); cancer detection

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## Introduction

Current methods of prostate cancer (PCa) screening and diagnosis have come under scrutiny because of their lack of diagnostic accuracy and performance. Historically, the current standard of care for prostate biopsy has been a 10–12 core transrectal ultrasound guided systematic biopsy (SB). The technique is lacking in diagnostic accuracy because of sampling error, and it's estimated that well less than 1% of the prostate is sampled during a prostate biopsy. Men with a persistent suspicion of PCa with one or more negative SB represents a diagnostic dilemma for urologists. Prostate multiparametric MRI (mpMRI) has been useful in this population by identifying suspicious prostate lesions, often in areas under-sampled by the SB. Currently the recommended mpMRI of the prostate consists of T1-weighted, high resolution T2-weighted images and at least

2 functional MRI techniques (1,2).

Targeted biopsy (TB) of suspicious lesions seen on MRI can be done cognitively under US guidance, performed in-gantry in a MRI suite, or using a MR/US fusion biopsy platform (3). Although debatable, under most circumstances concurrent SB continues to be performed at the time of TB biopsy given the occasional diagnosis of Gleason score  $\geq 7$  cancers uniquely identified to the SB alone (4). Many authors have found that MR fusion biopsy (which consists of TB + SB) is able to detect more clinically significant PCa (csPCa) than either modality alone, while many definitions of csPCa exist in the literature (5).

A growing body of literature has been in support of MR/US fusion biopsy, particularly in patients with a prior negative SB. Although the increased cost of this technology has been a concern, fusion biopsy technology has generally been gaining acceptance. In a recent survey

sent to members of Society of Urological Oncology, Endourological Society, European Association of Urology, 85.7% of respondents use prostate MRI in the practice and 63% use MR/US TB (6). Quality assurance is critical with adoption of this technology, since an institutional learning curve is associated with adoption of this technology (7).

## Methods

A PubMed and Web of Science database searches of peer reviewed literature using the following search terms (I) “magnetic resonance imaging” AND (“previous” or “prior” or “failed”) and “biopsy” and “PCa”; (II) “magnetic resonance imaging” and “PCa” and “biomarkers.” Over 1,100 articles were identified in the last 10 years and abstracts were screened for relevance. If relevance could not be determined by the abstract, then the full text was reviewed. Studies that included only biopsy-naïve patients were excluded from this review. Using relevance and quality of study design as criteria for inclusion, a total of 51 seminal articles on the topic of MR/US fusion TB in patients with a prior SB were selected by two authors by consensus to be included in this review

## Results

### *How does MR-US fusion TB with concurrent SB compare to SB alone in patients with a prior negative biopsy?*

Improved cancer detection rate (CDR), particularly CDR for csPCa, is frequently cited a rationale for use of MR fusion biopsy. The reported CDR for csPCa in men with a prior negative biopsy can range 20–40% and is lower compared to detection rates in biopsy-naïve patients (8,9). The attenuation in CDR is likely due to the reduced prevalence of higher volume disease in patients with a prior biopsy (10). Thus far, the vast majority of studies that favor TB + SB over SB in the prior negative biopsy cohort have used a retrospective or prospective cohort design (3,7,10-22) (Table 1). Currently, there are no published randomized controlled trials comparing the performance of TB + SB and SB in patients with at least one prior negative biopsy.

These cohort studies found that the TB + SB had a higher CDR for csPCa (typically defined as Gleason score  $\geq 7$ ) compared to the SB biopsy alone. The implication is that the TB is able to accurately sample cancerous areas of the prostate that are frequently missed on SB (20). In addition to increasing CDR, an additional advantage of fusion biopsy is the potential to reduce over detection of

clinically insignificant cancers. Siddiqui *et al.* reported MR/US fusion biopsy data on 1,003 men of which almost half were patients with prior negative biopsy. They found TB diagnosed 30% more high risk and 17% less low risk cancer than SB alone. In their cohort, there were significantly more anterior lesions seen in men with prior negative biopsy (19). Another group reported on their 1,042 patients who had undergone fusion biopsy, in which 324 had a prior negative biopsy. They found the combination of TB + SB was superior to either modality alone, with 61% of the men having cancer detected on TB + SB having Gleason  $\geq 7$ , versus 50% with SB alone (24). A study from the UK evaluated 54 men with at least one prior negative TRUS biopsy. All men had an mpMRI and then underwent a transperineal systematic prostate biopsies to determine the imaging accuracy in identifying cancer. They found sensitivities between 76–90% and negative predictive values between 75–95% for identify clinically significant cancer depending on the different definitions used (25). Researchers from UCLA previously reported on 105 patients with prior negative biopsies who went on to have a MRI/US fusion biopsy. They found that 91% of men with cancer found on TB had clinically significant cancer compared to only 54% with SB. MRI suspicion score was the most powerful predictor of identifying clinically significant cancer and independent of the number of prior negative biopsies (23).

Two separate meta-analyses found that the overall CDR of any PCa between TB + SB and SB did not significantly differ, but more csPCa and fewer insignificant cancers were detected with TB + SB. Although TB + SB may improve detection of significant PCa in men with previous negative biopsy, this has not consistently been shown in biopsy naïve men (8,26). A meta-analysis comparing MR fusion biopsy, SB, and perineal saturation biopsy suggested that fusion biopsy yielded the highest CDR and the lower number of cores needed to achieve cancer detection (27). According to a consensus statement by American Urological Association and the Society of Abdominal Radiology, use of MR/US guided biopsy after a prior negative biopsy is supported by the literature, but is contingent upon the availability and quality of MRI acquisition and interpretation (4).

These studies which report the CDR between TB + SB to SB in patients with prior negative biopsies can be difficult to compare directly because some only include patients with MRI visible lesions while others include patients with both positive and negative MRIs. Another limitation is the performance of concurrent SB at the time of MR/US fusion biopsy is used as a surrogate for SB alone, the gold standard reference remains final whole mount pathology,

Table 1 MR/US fusion biopsy studies comparing TB + SB versus SB alone in patients with a prior negative biopsy

References	No. Pts (regardless of indication)	No. Pts (prior negative biopsy)	Study design	MRI scanner	Endorectal coil	Reference standard	SB			TB + SB	
							CDR for any cancer (%)	CDR for csPCa (%)	CDR for any cancer (%)	CDR for csPCa (%)	
Abdi <i>et al.</i> (11)	172	172	Matched case control study	1.5-tesla	No	Biopsy results	22.1	16.3	41.9	34.9	
Brock <i>et al.</i> (12)	121	121	Prospective cohort study	3-tesla	Yes	Biopsy results	46.0	34.0	52.0	44.0	
Hambrock <i>et al.</i> (13)	71	71	Retrospective cohort study	3-tesla	Yes	Biopsy results	22.0	-	59.0	-	
Mariotti <i>et al.</i> (14)	389	143	Retrospective cohort study	3-tesla	Mixed	Biopsy results	41.0	12.6	51.0	26.6	
Martorana <i>et al.</i> (15)	157	157	Retrospective cohort study	1.5-tesla	Yes	Biopsy results	22.8	-	50.3	-	
Maxeiner <i>et al.</i> (16)	169	169	Prospective cohort study	3-tesla	No	Biopsy results	-	-	42.0	-	
Mendhiratta <i>et al.</i> (17)	161	161	Retrospective cohort study	3-tesla	No	Biopsy results	18.6	9.3	29.2	16.1	
Meng <i>et al.</i> (10)	601	172	Retrospective cohort study	3-tesla	No	Biopsy results	-	-	-	-	
Pinto <i>et al.</i> (3)	101	29	Prospective cohort study	3-tesla	Yes	Biopsy results	11.7	-	20.6	-	
Salami <i>et al.</i> (18)	140	140	Prospective cohort study	3-tesla	Yes	Biopsy results	48.6	30.7	52.1	47.9	
Siddiqui <i>et al.</i> (19)	1,003	432	Prospective cohort study	3-tesla	Yes	Biopsy results	-	-	-	-	
Sonn <i>et al.</i> (20)	171	65	Prospective cohort study	3-tesla	No	Biopsy results	-	-	37.0	-	
Sonn <i>et al.</i> (23)	94	94	Prospective cohort study	3-tesla	No	Biopsy results	26.6	13.8	22.3	20.2	
Truong <i>et al.</i> (7)	113	113	Retrospective cohort study	3-tesla	No	Biopsy results	41.6	25.7	52.2	41.6	
Volkin <i>et al.</i> (21)	162	92	Retrospective cohort study	3-tesla	Yes	Biopsy results	-	-	-	-	
Vourganti <i>et al.</i> (22)	195	195	Retrospective cohort study	3-tesla	Yes	Biopsy results	27.7	15.9	37.4	23.1	

TB, targeted biopsy; SB, systematic biopsy; CDR, cancer detection rate (derived from published data); csPCa, clinically significant prostate cancer (definitions vary).

but for obvious reasons that is not always possible. A non-randomized study utilized a matched cohort approach comparing MR TB versus SB alone without prior MRI to circumvent the potential bias of knowing where suspicious lesions were seen on mpMRI. The study found that MR TB diagnosed twice as many cases of clinically significant cancer without an increase in the diagnosis of clinically insignificant cancers (11).

A highly discussed topic regarding fusion biopsy studies is what actually constitute significant disease found on both MRI and fusion biopsy. Many studies apply definitions of csPCa typically used for systematic biopsies, but the most accurate identification of clinical significance is through comparison of prostatectomy pathology to that of the cancer detected by SB and fusion biopsy (28). One study suggested that the MRI-estimated lesion volume is associated with higher Gleason and stage at radical prostatectomy (15). The implication is that mpMRI is able to provide a better estimation of tumor volume and more accurately characterize the cancer.

Incorporating MRI into clinical practice does add additional cost; however, these additional costs can be offset by the reduction of costs associated with false positive biopsies and underestimation of tumor aggressiveness. In one study, a decision tree model based on Medicare reimbursements to compare the costs of TRUS biopsy versus fusion biopsy in men with prior negative biopsy (29). The MRI-based approach was most cost-effective for low risk patients (<30% probability of having cancer) and the cost savings found in the MRI group is related to the number of men which have negative MRIs and thus are spared a repeat biopsy. In another cost-effectiveness analysis, the cost of MRI/US fusion biopsy was comparable to SB. In this analysis, the costs were similar, but fusion biopsy led to an improvement in quality of life compared to SB due to the reduction in over diagnosis and subsequent treatment (30).

### *Anterior and apical tumors*

An advantage of fusion biopsy in patients with prior negative biopsy is the ability of MRI to identify suspicious lesions in areas not normally sampled by SB—specifically the anterior and apical parts of the prostate and thus the benefit of fusion biopsy is particularly accentuated in the prior negative biopsy cohort (17). A frequent observation is that csPCa is more frequently detected in the anterior prostate in the prior negative biopsy setting (31). One study evaluated the performance of fusion biopsy in the distal apical prostate, defined as the distal 6 mm apical portion of the prostate starting from the distal most visualized part of the prostate. They found that 80% of suspicious

lesions in this distal apical region were positive for cancer, and 33% of these patients had Gleason upgrading because of this TB (32). Another study found that among patients with a prior negative biopsy who underwent MR fusion biopsy, significantly more men with PCa identified on TB had anterior or apical lesions. In addition, of these patients that went on to have a radical prostatectomy, 86% had tumors at either the anterior or apex of the prostate (33). A different study concluded that in men with prior negative biopsies, not only were anterior lesions more common 70% *vs.* 30% peripheral zone, but that the majority, 93%, was intermediate-high risk (34).

MR fusion biopsy allows for more accurate characterization of the overall tumor burden, in part by its identification of anterior lesions. In one study, anterior lesions found on MRI with tumor involvement were 112% longer in the TB cores than in the concurrent SB cores (3.7 *vs.* 1.6 mm) (21). Racial differences have also been reported showing that African-American men with prior biopsy were twice as likely compared to white/other races to harbor cancer in the anterior prostate, suggesting that these men benefit even more from a MRI-based approach (35). Biopsy of anterior lesions can also be performed using transperineal approach. MR/US guided transperineal saturation biopsy has also been previously described with detection rates similar to transrectal approaches (36). In a comparative analysis of transperineal saturation biopsy versus FB after mpMRI, both methods had a similar detection rate for Gleason score  $\geq 7$  cancers, but FB reduced overdiagnosis of Gleason 3+3 cancers (37). Furthermore, a major advantage of FB over transperineal saturation biopsy is that FB does not require general anesthesia and can be performed in the clinic setting. Data is sparse regarding use of a transurethral biopsy approach after MRI. Recently, a study of a novel technique using transurethral resection to diagnose anterior located tumors identified on MRI allowed detection of Gleason score  $\geq 7$  cancers in 13/16 patients (38).

### *MRI reporting*

Due to significant variability in inter-observer MRI reads, PI-RADS Version 2 was recently developed in an effort to standardize image reporting by radiologists (39). In a recent meta-analysis, the pooled sensitivity and specificity for PIRADS scoring was 0.78 and 0.79, respectively, (40) which has been a substantial improvement over that of early studies (41,42). One study reported and improved AUC of as high as 0.86 for MRI/real-time elastography fusion in patients with prior negative biopsies (12). Currently, most

centers will perform targeted biopsies of lesions with a PIRADS score of 3–5, but knowing your own institution's biopsy performance and accuracy is paramount in guiding recommendations (4). A consensus statement also states at least 2 cores from each MRI target is recommended in patients undergoing FB after a prior negative biopsy (4). However, some groups have reported a higher CDR with an increasing number of cores obtained using TB in this patient population (7). CDR is variable across studies and is influenced by a variety of factors, including patient selection, accuracy of MRI reads, and targeting errors (43).

#### *How does mpMRI compare to other risk stratification tools?*

Currently, only a limited number of studies have directly compared the performance of mpMRI against clinical variables (PSA, DRE, PSAD), biomarkers, or nomograms. A PSAD of  $\leq 0.2$  was associated with low detection of Gleason score  $\geq 7$  in men with negative MRI and in men with equivocal imaging and may be useful for determining which men should opt for surveillance rather than repeat biopsy (44). In one study, the ability of mpMRI was directly compared against PHI and PCA3 for predicting biopsy outcome in the repeat biopsy setting (45). The combination of MRI + base model (DRE and PSA) had an AUC of 0.936 for predicting the presence of cancer at biopsy and was superior to PHI + base model or PCA3 + base model. Another study evaluated whether PCA3 could be combined with PIRADS version 1 score to predict a positive biopsy at the time of fusion biopsy after a previous negative SB. When PCA3 score is treated as a binary variable (PCA3 score  $> 80$ ), both PCA3 score and PIRADS score  $\geq 4$  predicted a positive repeat SB in a multivariate model (46). A small randomized study compared the use of PCA3 alone and PCA3+ FB in men with prior negative biopsy and found a marginal increase in the AUC (0.85 vs. 0.82) in the PCA+ FB arm (47). The current NCCN guidelines state that the following tests can be considered in patients thought to be at a higher risk despite a negative biopsy to inform the decision about performing a repeat biopsy: %f PSA, 4Kscore, PHI, PCA3, or ConfirmMDx.

A recent study found that mpMRI findings correlated well with Gleason score, but was not able to detect all aggressive PCas as defined by the Prolaris<sup>®</sup> CCP score. This study suggests that a combined molecular biomarker with radiomics (use of mpMRI-derived variables) in the future may provide the best sensitivity and specificity for significant disease (48). Whether these findings can be applied to men who have a prior negative biopsy undergoing fusion biopsy is unclear.

## Conclusions

Patients who have a prior negative biopsy and persistent suspicion of PCa represent a diagnostic dilemma for urologists. When a suspicious lesion is found on mpMRI, TB has consistently demonstrated improvement in clinically significant cancer detection compared to a repeat SB. Importantly, TB allows for better sampling of difficult to reach tumors in the anterior and apex of the prostate. In addition, fusion biopsy may be more cost-effective in the long-term by reducing the number of ineffective SBs and improving quality of life.

While the advances in MRI fusion biopsy technology are promising and an exciting area of research, urologists should be mindful of potential limitations of mpMRI. The performance of TB relies solely on the ability of mpMRI to identify clinically significant cancer, but mpMRI can miss small but significant tumors, and it is for this reason that TB + SB offers the best diagnostic accuracy (49). The observed increase in clinically significant cancer detection has been consistently demonstrated across cohort studies despite wide variations in MRI protocols and operator technique. It is for this reason that all men with a prior negative biopsy and continued suspicion of PCa should strongly be encouraged to get a prostate mpMRI prior to a repeat biopsy.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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