Magnetic Resonance Imaging-Ultrasound Fusion Targeted Prostate Biopsy in a Consecutive Cohort of Men with No Previous Biopsy: Reduction of Over Detection through Improved Risk Stratification

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Purpose: MRF-TB (magnetic resonance imaging-ultrasound fusion targeted prostate biopsy) may improve the detection of prostate cancer in men presenting for prostate biopsy. We report clinical outcomes of 12-core systematic biopsy and MRF-TB in men who presented for primary biopsy and further describe pathological characteristics of cancers detected by systematic biopsy and not by MRF-TB.

Materials and Methods: Clinical outcomes of 452 consecutive men who underwent prebiopsy multiparametric magnetic resonance imaging followed by MRF-TB and systematic biopsy at our institution between June 2012 and June 2015 were captured in an institutional review board approved database. Clinical characteristics, biopsy results and magnetic resonance imaging suspicion scores were queried from the database.

Results: Prostate cancer was detected in 207 of 382 men (54.2%) with a mean ± SD age of 64 ± 8.5 years and mean ± SEM prostate specific antigen 6.8 ± 0.3 ng/ml who met study inclusion criteria. The cancer detection rate of systematic biopsy and MRF-TB was 49.2% and 43.5%, respectively ($p = 0.006$). MRF-TB detected more Gleason score 7 or greater cancers than systematic biopsy (117 of 132 or 88.6% vs 102 of 132 or 77.3%, $p = 0.037$). Of 41 cancers detected by systematic biopsy but not by MRF-TB 34 (82.9%) demonstrated Gleason 6 disease, and 26 (63.4%) and 34 (82.9%) were clinically insignificant by Epstein criteria and a UCSF CAPRA (University of California-San Francisco-Cancer of the Prostate Risk Assessment) score of 2 or less, respectively.

Conclusions: In men presenting for primary prostate biopsy MRF-TB detects more high grade cancers than systematic biopsy. Most cancers detected by systematic biopsy and not by MRF-TB are at clinically low risk. Prebiopsy magnetic resonance imaging followed by MRF-TB decreases the detection of low risk cancers while significantly improving the detection and risk stratification of high grade disease.

Key Words: prostatic neoplasms, magnetic resonance imaging, ultrasonography, biopsy, diagnostic imaging

Abbreviations and Acronyms

CDR = cancer detection rate

GS = Gleason score

mpMRI = multiparametric MRI

MRGB = MRI guided targeted biopsy

MRI = magnetic resonance imaging

mSS = maximum MRI suspicion score

PCa = prostate cancer

PSA = prostate specific antigen

SB = systematic biopsy

US = ultrasound

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PROSTATE cancer is the most common cancer diagnosed in men in the United States and the second most common cause of cancer death.[1] Traditional US guided prostate biopsy has been shown to have limited sensitivity for detecting PCa.[2,3] Consequently an initial biopsy negative for PCa often does not reliably indicate absent disease.[4] Additionally in light of the increasing number of prostate biopsies performed due to increased PSA[5] the rate of over detection of clinically low risk disease varies from 2% to 67% of cancer diagnoses,[6] leading to unnecessary morbidity associated with overtreatment and decreased quality of life.[7,8]

Current evidence demonstrates improved sensitivity for detecting high grade PCa using mpMRI followed by MRI targeted biopsy than with standard 12-core systematic biopsy.[9–12] We compared the outcomes of targeted prostate biopsy performed with automated MRI-US fusion and 12-core SB done with a computerized template in the population of men with increased PSA and no history of prostate biopsy. In light of recent evidence suggesting that MRI targeted biopsy selectively identifies high grade cancer compared to SB[13] we further characterized cancers that were missed or mischaracterized as low grade by MRF-TB alone.

MATERIALS AND METHODS

Study Design and Population

Between June 2012 and June 2015, 675 consecutive men with no prior biopsy who presented to our institution for prostate biopsy were offered prebiopsy mpMRI. No abnormality was identified in 100 (14.2%) of these men. Of the remaining 575 men 452 (78.6%) proceeded to combined MRF-TB and SB. Clinical data mSS and biopsy results were recorded in an institutional review board approved database (fig. 1). Some men were excluded from analysis, including 20 who underwent MRI with a nonstandard prostate MRI protocol and 50 in whom the prebiopsy mpMRI was not read according to standardized trial reporting criteria.

Multiparametric MRI

mpMRI was performed using a 3 Tesla whole body system and a pelvic phased array coil. It included multiplanar turbo-spin echo T2-weighted images, axial single shot echo-planar imaging diffusion-weighted imaging with b-values of 50 and 1,000 seconds per mm^2, and dynamic contrast enhanced imaging MRI after intravenous administration of gadolinium chelate. Before biopsy MRI studies were reviewed by a single fellowship trained radiologist with 5 to 6 years of experience with prostate MRI at the time of this study to identify suspicious foci in the prostate. The probability of tumor was scored on a 5-point Likert scale, including mSS 2—low probability, 3—equivocal, 4—high probability and 5—very high probability as previously reported.[10,14,15] Studies with no identified suspicious region received a score of 1 and were not candidates for MRI targeted biopsy.

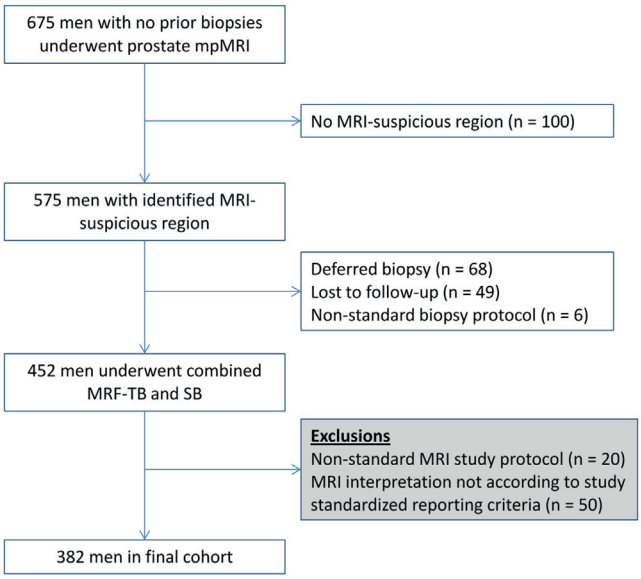

Figure 1. Patient enrollment

MRI-US Fusion Targeted Biopsy

MRF-TB was done with the Artemis™ ProFuse co-registration system for mpMRI segmentation, co-registration of MRI to US images and 3-dimensional biopsy planning as described in our previous study.[10] Briefly lesion boundaries were identified by the radiologist on T2-weighted images and transferred to the Artemis system for guidance during the biopsy procedure. Computer assisted co-registration of segmented MRI and US images of the prostate was performed by manual rigid translation followed by automated elastic deformation. With the patient in the left lateral decubitus position transrectal biopsies were obtained beginning with 4 biopsy cores targeted to each suspicious lesion identified on MRI and followed by 12-core computerized template biopsy with core locations designated by the Artemis generated template. Procedures were done using the Pro Focus™ or Noblus (Hitachi Aloka Medical America, Wallingford, Connecticut) US system, an end fire probe, a reusable biopsy gun, 18 gauge needles and local anesthesia with 1% lidocaine infiltration.

For each patient all systematic and targeted biopsies were performed by the same 1 of 4 faculty physicians with expertise in prostate biopsy. All biopsy cores were analyzed by specialized genitourinary pathologists at the same single institution.

Data Analysis and Statistics

Biopsy results were compared using the highest GS obtained by each technique. Determination of high grade cancer was based on GS 7 or greater. Clinically insignificant cancer was assessed using Epstein criteria[16] and a UCSF CAPRA score of 2 or less.[17] Other comparative data points included the number of biopsy cores demonstrating cancer, cancer core length per core and the percent of Gleason pattern 4 disease.

All analysis was done in SPSS®, version 21.0. Categoric variable comparisons were performed with the chi-square test and continuous variables were evaluated with the Student t-test. Comparison of cancer detection rates between techniques was assessed by the McNemar test.

RESULTS

A total of 382 men met study inclusion criteria. Table 1 lists additional patient characteristics.

Overall Cancer Detection

PCa was identified in 207 men (54.2%). The CDR of SB and MRF-TB was 49.2% and 43.5%, respectively ($p = 0.006$). GS 7 or greater cancer was detected in 132 men (34.6%). Table 2 lists the CDRs of GS 6 and 7 or greater disease for each biopsy technique. MRF-TB detected more GS 7 or greater cancers than SB (117 of 132 or 88.6% vs 102 of 132 or 77.3%, $p = 0.037$). MRF-TB contributed to a 29% increase in GS 7 or greater PCa detection compared to SB while SB contributed to a 12% increase in GS 7 or greater PCa detection compared to MRF-TB. Nine of the 15 GS 7 or greater cancers (60%) detected by SB that were missed or graded as GS 6 by MRF-TB demonstrated minimal pattern 4 (GS 3 + 4) disease in only 1 SB core. MRF-TB diagnosed more GS 7 or greater disease using fewer cores per prostate than SB (table 3).

Detection of Clinically Low Risk Disease

While SB detected more cancers than MRF-TB, 34 of 41 cancers (82.9%) detected by SB but not by MRF-TB were GS 6 while 26 of 41 (63.4%) and 34 of 41 (82.9%) were clinically insignificant by Epstein criteria[16] and a UCSF CAPRA score of 2 or less,[17] respectively. In contrast 8 of 19 cancers (42.1%) detected by MRF-TB but not by SB showed GS 6 cancer, and only 3 (16.0%) and 6 of 19 (31.6%) were clinically insignificant by Epstein[16] and UCSF CAPRA[17] criteria, respectively. Consequently compared to cancers detected only by MRF-TB a higher proportion detected only by SB were GS 6 ($p = 0.001$), and clinically insignificant by Epstein and UCSF CAPRA criteria (each $p < 0.001$, fig. 2).[16,17] Table 4 lists descriptive features of discordant SB and MRF-TB results. Ultimately SB contributed to the detection of 34 additional GS 6 cancers while detecting only 5 with GS 7 or greater (4 + 3) or GS 7 (3 + 4) in more than 1 core missed by MRF-TB.

Table 1. *Patient demographics*

No. pts	382	
Mean ± SD age	64.5 ± 8.4	
Mean ± SEM PSA (ng/ml)	6.8 ± 0.3	
Median cc MRI prostate vol (IQR)	44 (36–64)	
No. MRI abnormalities (%):		
1	238	(62.3)
2	123	(32.2)
3	19	(5.0)
4	2	(0.5)
No. mSS (%):		
2	115	(30.1)
3	118	(30.9)
4	78	(20.4)
5	71	(18.6)

Table 2. *Comparative outcomes of MRF-TB and SB*

	No. MRF-TB (%)			
SB	Gleason 7 or Greater	Gleason 6	No Ca	Total No.
GS 7 or greater	87 (22.8)	8 (2.1)	7 (1.8)	102 (26.7)*
GS 6	19 (5.0)	33 (8.6)	34 (8.9)	86 (22.5)†
No Ca	11 (2.9)	8 (2.1)	175 (45.8)	194 (50.8)
Totals	117 (30.6)*	49 (12.8)†	216 (56.5)	382 (100)

*$p = 0.037$.
†$p < 0.001$.

MRI Suspicion Score and PCa Detection

Table 5 lists CDRs by mSS. Of 149 men with mSS 4 or greater 128 (85.9%) were found to have PCa. In this subgroup of 149 men 103 (69.1%) were found to have GS 7 or greater cancer. MRF-TB did not detect 7 of these 103 cancers (6.8%) and SB did not detect 25 (24.3%) ($p < 0.001$). Of 233 men with mSS 2 or 3 the GS was 7 or greater (3 + 4) and 7 or greater (4 + 3) in 29 (12.4%) and 10 (4.3%), respectively. In 5 of these 29 men (17.2%) GS 7 (3 + 4) cancers and in 1 of 8 (12.5%) GS 7 or greater (4 + 3) cancers were missed or classified as GS 6 by MRF-TB. Of 31 cancers detected by SB that were not detected by MRF-TB in men with mSS 2 or 3, 18 (58.0%) and 24 (77.4%) were clinically insignificant by Epstein[16] and UCSF CAPRA[17] criteria, respectively.

Using a cutoff of mSS 4 or greater the sensitivity, specificity, and negative and positive predictive values for detecting GS 7 or greater PCa with combined MRF-TB and SB were 78.0%, 81.6%, 87.6% and 69.1%, respectively.

DISCUSSION

The goals of prostate biopsy in men with clinical suspicion of PCa have changed in recent years. While cancer detection remains of paramount

Table 3. *Biopsy characteristics by technique*

	MRF-TB	SB
Mean No. biopsy cores:		
Per prostate	5.7	12.0
To diagnose 1 GS 7 or greater Ca	18.8	44.9
No. max GS (%):		
No Ca	216 (56.5)	194 (50.7)
3 + 3	49 (12.8)	86 (22.5)
3 + 4	62 (16.2)	40 (10.5)
4 + 3 or Greater	55 (14.4)	62 (16.2)

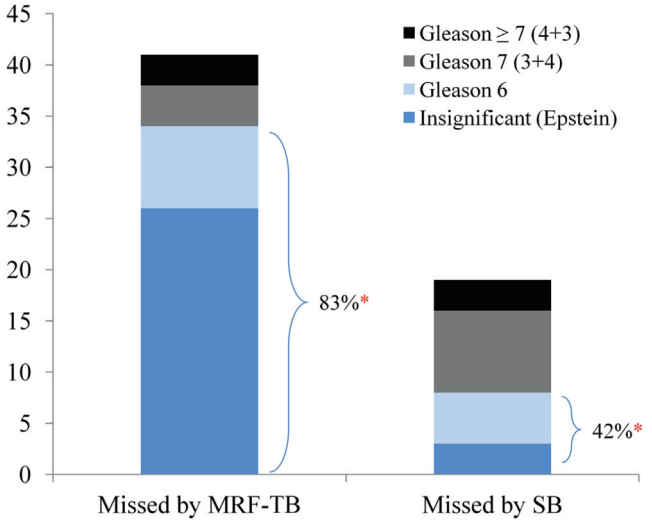

Figure 2. PCa missed by MRF-TB and SB. Asterisk indicates MRF-TB vs SB detection of GS 6 cancer p <0.001.

importance, there is a growing desire to decrease the detection of indolent, potentially nonlethal cancers.[18] Various biomarkers and imaging techniques are available that aim to discriminate men with regard to the risk of high grade cancer but the optimal implementation of these tools in clinical practice remains unclear.[19,20] Recent evidence has supported prebiopsy MRI to improve the detection of high risk cancer in men who present for a first prostate biopsy.[21] In our cohort of men without previous biopsy prebiopsy mpMRI followed by MRF-TB provided overall better detection of high grade cancer than SB while limiting the detection of cancer with low risk features.

Mozer et al reported the outcomes of comparing MRF-TB with extended 12-core systematic biopsy in men with no previous biopsies.[22] In a cohort of 152 men overall CDR was lower for MRF-TB than for SB (54% vs 57%) as we noted in our study. There was almost no difference in the detection of GS 7 or greater cancers between the 2 techniques in their biopsy results (21.7% vs 22.4%). However, when categorized as clinically significant disease (at least 1 core with GS 3 or greater + 4 or 6 with a maximum cancer core length of 4 mm or greater) vs clinically insignificant disease, MRF-TB detected more significant cancers than SB (43.4% vs 36.8%).

Delongchamps et al also reported outcomes of prebiopsy MRI and targeted biopsy vs standard transrectal biopsy in 391 men who presented for the first biopsy.[23] Of 264 men who underwent targeted biopsy using rigid or elastic co-registration of MRI and US images targeted biopsy demonstrated higher GS 7 or greater cancer detection than standard biopsy. In these 2 groups but not in the visual co-registration group targeted biopsy also yielded higher overall cancer detection than standard biopsy. Pokorny et al reported the results of MRGB vs standard transrectal biopsy in biopsy naive men.[11] Of 142 men with abnormal mpMRI, defined as a PI-RADS (Prostate Imaging Reporting and Data System) score of 3 or greater, PCa was detected by standard biopsy in 101 (71.1%) vs 99 (69.7%) by MRGB. However, MRGB detected more high risk cancer than standard biopsy (65.5% vs 52.1%).

When interpreting the published literature on MRI targeted biopsy, critical concepts regarding the value of targeted biopsy should be considered. Past series have shown higher overall CDR than ours,[11,22,23] which may suggest differences in the underlying prevalence and stage of disease among tested cohorts. The relative added benefit of MRI targeting likely varies with cancer prevalence as SB is more likely to identify cancer in men with high prevalence and more advanced stage of disease. Additionally the definitions of clinical significance currently reported are to some extent arbitrary with inadequate correlation with eventual disease outcome. In this regard reporting standards can greatly influence the outcome of the study and inflate the perceived impact of targeting. While to our knowledge previously reported measures of clinical significance have not been validated in the setting of MRI targeted biopsy, we used several of these definitions to better illustrate the significance of disease.

Table 4. *Discordant results between MRF-TB and SB*

		No. Max GS (%)				No. Max SB Core Ca (%)			No. mSS (%)	
Max GS Detected	No. Pts	6	7 (3 + 4)	7 (4 + 3)	8 or Greater	10% or Less	10%—50%	50% or Greater	2 or 3	4 or 5
By SB vs MRF-TB:	49	34 (69)	9 (18)	5 (10)	1 (2)	20 (41)	20 (41)	9 (18)	32 (65)	17 (35)
7 or Greater vs 6	8	—	5 (63)	3 (37)	0 (0)	1 (13)	3 (37)	4 (50)	3 (37)	5 (63)
7 or Greater vs neg	7	—	4 (57)	2 (29)	1 (14)	2 (29)	4 (57)	1 (14)	3 (53)	4 (57)
6 vs neg	34	34 (100)	—	—	—	17 (50)	13 (38)	4 (12)	26 (76)	8 (24)
By MRF-TB vs SB:	38	8 (21)	21 (55)	9 (24)	1 (3)	5 (13)	5 (13)	28 (74)	11 (29)	27 (71)
7 or Greater vs 6	19	—	12 (63)	6 (32)	1 (5)	0 (0)	4 (21)	15 (79)	2 (11)	17 (89)
7 or Greater vs neg	11	—	8 (73)	3 (27)	0 (0)	1 (9)	1 (9)	9 (82)	2 (18)	9 (82)
6 vs Neg	8	8 (100)	—	—	—	4 (50)	0 (0)	4 (50)	7 (88)	1 (12)

Table 5. *Cancer detection rate by mSS*

mSS (approach)	No. Pts	No. Max GS (%)		No. Neg (%)
		7 or Greater	6	
4 or 5:	149	103 (69.1)	25 (16.8)	21 (14.1)
MRF-TB		96 (63.8)*	22 (14.8)	31 (20.8)
SB		78 (52.3)*	40 (26.8)	31 (20.8)
2 or 3:	233	29 (12.4)	50 (21.5)	154 (66.1)
MRF-TB		21 (9.0)	27 (11.6)†	185 (79.4)
SB		24 (10.3)	46 (19.7)†	163 (70.0)

* $p = 0.003$.
† $p = 0.002$.

To our knowledge this study represents the largest reported cohort of biopsy naive men undergoing MRI-US software fusion targeted and 12-core systematic prostate biopsy. This analysis was intended to investigate differences between cancers detected by traditional 12-core SB and by MRF-TB using a MRI-US fusion platform in men with mpMRI visualized lesions suspicious for PCa and use the information derived to inform biopsy practice. By yielding a lower rate of overall cancer detection but a higher rate of GS 7 or greater cancer detection compared to SB our outcomes of MRF-TB reflect the trends reported in other MRI guided prostate biopsy trials. They also demonstrate a significant reduction in low risk PCa detection with MRF-TB.

Because the problem of over detection of low risk disease by traditional biopsy methods has prompted an effort to selectively identify high risk PCa, an approach is to consider the relative contribution of SB to MRF-TB outcomes. A larger proportion of PCa detected by MRF-TB was found to be high grade compared to that detected by SB, including 22% diagnosed as low grade by SB and 11 men in whom SB detected no cancer. Importantly we noted that 63% to 82% of PCa detected by SB and missed by MRF-TB in biopsy naïve men were likely to be clinically insignificant. Conversely as few as 16% of PCas detected by MRF-TB and not by SB were clinically insignificant. Even among GS 7 or greater PCas detected by SB that were missed or graded as GS 6 by MRF-TB most lesions demonstrated a minimal Gleason pattern 4 component, suggesting that these men represent the lower end of the spectrum of intermediate risk. Had all men in this study undergone MRF-TB alone, the detection of up to 34 clinically insignificant cancers would have been avoided and only 5 cancers with GS 7 or greater (4 + 3) or GS 7 (3 + 4) in more than 1 core would have been missed among 382 men.

Additionally by considering the relative contribution of SB in men stratified by mSS it may be possible to further optimize the balance between high grade PCa detection and avoidance of low risk disease. Of 34 clinically insignificant cancers detected by SB and missed by MRF-TB 24 (70.1%) were detected in men with mSS less than 4. Only 4 GS 7 or greater cancers were detected by SB alone in this subgroup of 233 men. Therefore, prebiopsy MRI followed by targeted biopsy and avoidance of systematic biopsy in select men, especially those with mSS 2 or 3, may provide the greatest potential to limit the detection of low risk cancer while maximizing the detection of high grade disease.

This study benefited from institutional experience with prostate MRI, the fact that all mpMRIs were interpreted and scored by a single experienced radiologist and the standardized biopsy approach performed by a few experienced operators. Limitations of our study include the potential for selection bias, given its retrospective nature and the referral pattern of our practice. We believe that the consecutive nature of our cohort to an extent minimizes the possibility of bias as men were largely referred based on community screening practices. Additionally our conclusions regarding disease risk are based purely on biopsy and were not validated by prostatectomy. Due to current practices of selectively offering prostatectomy to patients at higher risk such a study may not be feasible. Disease risk in our study was defined based on risk stratification methods derived from systematic biopsy. As such they may not be valid in the setting of MRF-TB. Despite this we believe they offer the best known means to assess risk in the biopsy setting. Finally because outcomes of biopsy in men with normal MRI were not included in this analysis, the impact of avoiding biopsy in those men could not be measured in our study. However, based on our early experience suggesting a high negative predictive value of normal MRI[24] we believe that the likelihood of missing significant disease in this population is low.

Despite the inherent limitations of our analysis we strongly believe that the outcomes of this study support the practice of prebiopsy MRI followed by selective targeted biopsy as a tool to maximize the identification of high grade cancer and limit the detection of indolent disease in the group of men with abnormal MRI.

CONCLUSIONS

In men with increased PSA who present for initial prostate biopsy prebiopsy mpMRI followed by MRF-TB in those with suspicious MRI limits over detection of clinically insignificant PCa while providing greater detection of clinically significant PCa than SB alone. The majority of PCas detected by SB but missed by MRF-TB represent clinically insignificant disease based on several definitions. mpMRI provides added ability to predict the risk of

GS 7 or greater cancer with a negative predictive value of 88% for detecting GS 7 or greater disease in men with a maximum mSS of 2/3 and a positive predictive value of 69% in men with a maximum mSS of 4/5. Prebiopsy mpMRI is an effective tool for further risk stratification in men with clinical suspicion of prostate cancer and no previous biopsy.

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