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Prostate Cancer

Relationship Between Prebiopsy Multiparametric Magnetic Resonance Imaging (MRI), Biopsy Indication, and MRI-ultrasound Fusion–targeted Prostate Biopsy Outcomes

Xiaosong Meng[a], *Andrew B. Rosenkrantz*[b], *Neil Mendhiratta*[c], *Michael Fenstermaker*[c], *Richard Huang*[a], *James S. Wysock*[a,e], *Marc A. Bjurlin*[a,f], *Susan Marshall*[a], *Fang-Ming Deng*[d], *Ming Zhou*[d], *Jonathan Melamed*[d], *William C. Huang*[a], *Herbert Lepor*[a], *Samir S. Taneja*[a,b,*]

[a] *Department of Urology, NYU Langone Medical Center, New York, NY, USA;* [b] *Department of Radiology, NYU Langone Medical Center, New York, NY, USA;* [c] *School of Medicine, NYU Langone Medical Center, New York, NY, USA;* [d] *Department of Pathology, NYU Langone Medical Center, New York, NY, USA;* [e] *Department of Urology, New York Hospital Queens, Flushing, NY, USA;* [f] *Department of Urology, St. Barnabas Hospital, Bronx, NY, USA*

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Abstract

Background: Increasing evidence supports the use of magnetic resonance imaging (MRI)-ultrasound fusion–targeted prostate biopsy (MRF-TB) to improve the detection of clinically significant prostate cancer (PCa) while limiting detection of indolent disease compared to systematic 12-core biopsy (SB).
Objective: To compare MRF-TB and SB results and investigate the relationship between biopsy outcomes and prebiopsy MRI.
Design, setting, and participants: Retrospective analysis of a prospectively acquired cohort of men presenting for prostate biopsy over a 26-mo period. A total of 601 of 803 consecutively eligible men were included.
Interventions: All men were offered prebiopsy MRI and assigned a maximum MRI suspicion score (mSS). Men with an MRI abnormality underwent combined MRF-TB and SB.
Outcomes: Detection rates for all PCa and high-grade PCa (Gleason score [GS] $\geq$7) were compared using the McNemar test.
Results and limitations: MRF-TB detected fewer GS 6 PCas (75 vs 121; $p < 0.001$) and more GS $\geq$7 PCas (158 vs 117; $p < 0.001$) than SB. Higher mSS was associated with higher detection of GS $\geq$7 PCa ($p < 0.001$) but was not correlated with detection of GS 6 PCa. Prediction of GS $\geq$7 disease by mSS varied according to biopsy history. Compared to SB, MRF-TB identified more GS $\geq$7 PCas in men with no prior biopsy (88 vs 72; $p = 0.012$), in men with a prior negative biopsy (28 vs 16; $p = 0.010$), and in men with a prior cancer diagnosis (42 vs 29; $p = 0.043$). MRF-TB detected fewer GS 6 PCas in men with no prior biopsy (32 vs 60; $p < 0.001$) and men with prior cancer (30 vs 46; $p = 0.034$). Limitations include the retrospective design and the potential for selection bias given a referral population.
Conclusions: MRF-TB detects more high-grade PCas than SB while limiting detection of GS 6 PCa in men presenting for prostate biopsy. These findings suggest that prebiopsy multiparametric MRI and MRF-TB should be considered for all men undergoing prostate biopsy. In addition, mSS in conjunction with biopsy indications may ultimately help in identifying men at low risk of high-grade cancer for whom prostate biopsy may not be warranted.
Patient summary: We examined how magnetic resonance imaging (MRI)-targeted prostate biopsy compares to traditional systematic biopsy in detecting prostate cancer among men with suspicion of prostate cancer. We found that MRI-targeted biopsy detected more high-grade cancers than systematic biopsy, and that MRI performed before biopsy can predict the risk of high-grade cancer.

* Corresponding author. Department of Urology and Radiology, NYU Langone Medical Center, New York, NY 10016, USA. Tel. +1 646 8256321; Fax: +1 646 8256399.
E-mail address: samir.taneja@nyumc.org (S.S. Taneja).

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1. Introduction

Increasing evidence supports the use of prebiopsy multiparametric magnetic resonance imaging (mpMRI) for disease localization to address many of the limitations of systematic biopsy (SB), most importantly by improving the detection of clinically significant prostate cancer (PCa) while potentially limiting the detection of indolent disease [1–4]. MRI-targeted biopsy, using cognitive or software-based fusion of prostate MRI and real-time ultrasound (US) images, increases the detection of clinically significant PCa using fewer cores than SB [2,5], while potentially reducing the detection of low-grade cancers that are unlikely to affect a man's longevity. Prebiopsy mpMRI allows accurate tumor localization [6] and grading of cancer suspicion using an MRI suspicion score (mSS), and thus provides accurate prediction of the likelihood of PCa on prostate biopsy [7] that correlates with cancer aggressiveness [8] before biopsy.

Here we report outcomes of MRI-targeted prostate biopsy using MRI-US fusion (MRF-TB) compared to 12-core SB among all men who presented consecutively at our institution for prostate biopsy over a 26-mo period. We explore the relationship between prebiopsy MRI findings and clinical biopsy indication and MRF-TB and SB outcomes with the aim of optimizing the current PCa diagnostic pathway by identifying before biopsy those men for whom prostate biopsy has a low diagnostic yield.

2. Patients and methods

2.1. Study design and population

Between June 2012 and August 2014, all men presenting to our institution for prostate biopsy were recommended to undergo prebiopsy mpMRI to identify areas within the prostate suspicious for cancer, unless medically contraindicated. A total of 803 men underwent mpMRI followed by prostate biopsy, and outcomes were recorded in a database approved by the institutional review board. Before biopsy, MRI results for all patients were reviewed by a single fellowship-trained radiologist with expertise in prostate imaging to identify and score suspicious regions within the prostate using a 5-point Likert scale for cancer suspicion, as previously described [6,9]. For each patient, SB and MRF-TB were performed by one of four faculty urologic oncologists experienced in prostate biopsy. Biopsy cores were interpreted by one of three genitourinary pathologists.

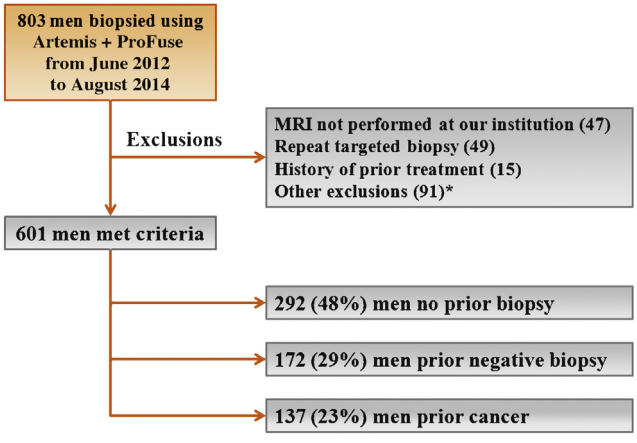

Fig. 1 – Study flow diagram. MRI = magnetic resonance imaging. * Other exclusions are listed in the text.

We collected data on clinical characteristics, biopsy history, biopsy indication, prostate-specific antigen, mSS, and histopathologic results for SB and MRF-TB for all men who underwent biopsy in the study period. Men were excluded from the analysis if their MRI study was not performed at our institution ($n = 47$), had a repeat MRF-TB after already being included in the cohort ($n = 49$), had prior treatment for PCa ($n = 15$), and for other reasons, including nonstandard MRI protocols, 1.5-T MRI studies, artifacts caused by hip orthopedic hardware, or missing data elements ($n = 91$; Fig. 1). For 125 men in the cohort who were also included in the PROFUS trial [5] comparing two co-registration–guided and two cognitively directed cores, all four cores were grouped as MRI-targeted cores. In total, 601 patients were included in the final cohort analysis.

2.2. mpMRI

MRI was performed using a 3-T clinical MRI instrument and an external phased-array coil and included multiplanar T2-weighted images, axial diffusion-weighted imaging using b values of 50 and 1000 s/mm^2, and dynamic contrast-enhanced imaging after intravenous administration of a gadolinium chelate. Lesions identified on MRI were scored as 2 (low probability), 3 (equivocal), 4 (high probability), or 5 (very high probability), as previously described [5,9,10]. Men with mSS = 1 (no findings suspicious for cancer) were not candidates for targeted biopsy and thus were not included in this analysis. For men with multiple lesions with differing mSS values, the highest mSS for any individual lesion was recorded as representing the overall mSS for the patient.

2.3. MRF-TB

MRF-TB was performed using an Artemis prostate biopsy system and ProFuse (Eigen, Grass Valley, CA, USA) software for mpMRI segmentation, co-registration of MRI and US images, and three-dimensional biopsy planning, as previously described [5]. T2-weighted MRI sequences in which the suspicious lesions were outlined were loaded onto the Artemis biopsy device. Computer-assisted co-registration of segmented MRI and US images of the prostate was performed using manual rigid translation followed by automated elastic deformation. Transrectal biopsies were obtained with the patient in the left lateral decubitus position, beginning with four biopsy cores targeted to each suspicious lesion identified on mpMRI and followed by 12 software-populated, spatially distributed cores. Sites for 12-core sampling were selected by the Artemis device, not the operating surgeon. The procedures were performed using a Pro Focus (BK Medical, Peabody, MA, USA) or Noblus ultrasound system (Hitachi Aloka Medical America, Wallingford, CT, USA), an endfire probe, a reusable biopsy gun, 18G biopsy needles, and local anesthesia with 1% lidocaine infiltration.

2.4. Statistical analysis

Univariable categorical variables were compared using the χ^2 test and continuous variables were evaluated using the Student t test after evaluating the normality of the data via a one-sample Kolmogorov-Smirnov test. The McNemar test was used to evaluate differences in cancer detection rates between MRF-TB and SB. One-way analysis of variance was used to compare continuous variables between groups unless the data were not normally distributed, in which case the Kruskal-Wallis test was used. The Cochran-Armitage trend test was used to calculate the relationship between mSS and CDR. For each test result, a corresponding two-tailed p-value <0.05 was considered a statistically significant finding. All analysis was carried out using SPSS v.21.0 software (IBM Corp., Armonk, NY, USA).

Table 1 – Patient characteristics

	Total	NPB	PNB	PCD	*p* value
Patients (*n*)	601	292	172	137	
Mean age, yr (SD)	65.2 (8.0)	64.4 (8.4)	65.9 (7.5)	66.3 (7.7)	0.033
Mean PSA, ng/ml (SEM)	6.7 (.3)	6.2 (.4)	8.9 (0.7)	5.4 (0.4)	<0.001
Mean BMI, kg/m^2 (SD)	27.1 (4.3)	27.1 (4.4)	27.0 (3.4)	27.1 (4.8)	0.963
Mean prostate volume, cm^3 (SD)	59.9 (38.2)	53.1 (27.2)	76.9 (44.4)	53.4 (42.2)	<0.001
Mean MRI suspicious regions, *n* (SD)	1.58 (0.66)	1.63 (0.66)	1.56 (0.65)	1.51 (0.64)	0.213
Mean maximum mSS (SD)	3.3 (1.0)	3.3 (1.1)	3.1 (1.0)	3.3 (1.0)	0.144

NPB = no prior biopsy; PNB = prior negative biopsy; PCD = prior cancer diagnosis; SD = standard deviation; PSA = prostate-specific antigenl SEM = standard error of the mean; MRI = magnetic resonance imaging; mSS = MRI suspicion score.

Table 2 – Concordance of cancer detection between SB and TB in all patients

Systematic biopsy	Cancer detection, *n* (%)				
	Targeted biopsy				
	GS ≥ 4 + 3	GS 3 + 4	GS 6	No cancer	Total
GS ≥ 4 + 3	42 (7)	8 (1)	2 (2)	2 (<1)	54 (9) *
GS 3 + 4	4 (1)	39 (6)	13 (2)	7 (1)	63 (10) †
GS 6	3 (<1)	20 (3)	37 (6)	61 (10)	121 (20) ‡
No cancer	20 (3)	22 (4)	23 (4)	298 (50)	363 (60)
Total	69 (11) *	89 (15) †	75 (12) ‡	368 (61)	601 (100)

GS = Gleason score.
* $p < 0.05$ SB versus TB for GS ≥7 (4 + 3) prostate cancer.
† $p < 0.05$ SB versus TB for GS 7 (3 + 4) prostate cancer.
‡ $p < 0.05$ SB versus TB for GS 6 prostate cancer.

3. Results

3.1. Study population

Among 601 men, 292 (48%) had no prior prostate biopsy (no prior biopsy group), 172 (29%) had a prior negative prostate biopsy (prior negative biopsy group), and 137 (23%) had been previously diagnosed on SB with low-volume Gleason 6 cancer and were under consideration for active surveillance after risk stratification biopsy (prior cancer diagnosis group; Table 1). The mSS was 2 in 171 (29%), 3 in 196 (33%), 4 in 144 (24%), and 5 in 90 (15%) men. The mSS distribution did not differ among the three groups ($p = 0.123$).

3.2. Cancer detection rates for the whole cohort

For detection of all PCas, MRF-TB was similar to SB ($p = 0.731$). However, MRF-TB detected significantly fewer Gleason 6 ($p < 0.001$) and significantly more Gleason ≥7 cancers ($p < 0.001$) compared to SB. MRF-TB also detected significantly more Gleason dominant pattern 4 PCas compared to SB ($p = 0.025$). Table 2 shows differences in detection for high-grade and low-grade cancer. Among the 61 men with GS 6 on SB and no cancer detected on MRF-TB, only two had more than three positive cores and only four had >50%/core (Supplementary Table 1).

3.3. Cancer detection rates stratified by biopsy indication

To assess the relationship between biopsy indication and cancer detection rates, men were evaluated separately by group (Fig. 2). MRF-TB detected more GS ≥7 PCa in all three groups. In the group with no prior biopsy, although MRF-TB detected significantly more GS ≥7 than SB ($p = 0.012$), the overall lower detection rate for MRF-TB was due to significantly lower detection of GS 6 PCa (32 vs 60 men; $p < 0.001$). In the group with a prior negative biopsy, MRF-TB detected significantly more GS ≥7 PCas compared to SB (28 vs 16 men; $p = 0.010$), but there was no difference in detection of GS 6 PCas ($p = 0.838$). In the group with a prior cancer diagnosis, overall PCa detection was similar between MRF-TB and SB, but MRF-TB detected significantly more GS ≥7 PCas ($p = 0.043$) and significantly fewer GS 6 PCas ($p = 0.034$) compared to SB (Supplementary Table 2). Of all cancers detected by MRF-TB alone, 9/21 (43%), 11/22 (50%), and 10/22 (45%) were located in the anterior prostate in

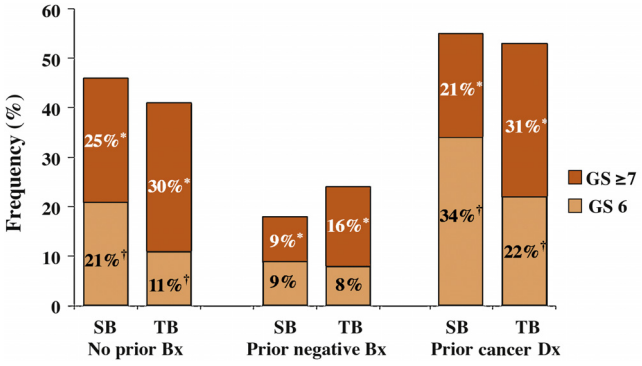

Fig. 2 – Comparison of detection of GS ≥7 and GS 6 cancers between SB and MRF-TB stratified by biopsy indication. * $p < 0.05$, SB vs MRF-TB for GS ≥7; † $p < 0.05$, SB vs MRF-TB for GS 6. GS = Gleason score; SB = systematic biopsy; MRF-TB = magnetic resonance imaging-ultrasound fusion–targeted biopsy; Bx = biopsy; Dx = diagnosis.

Table 3 – Cancer detection rate by magnetic resonance imaging suspicion score (mSS) within each group

mSS	Men, *n* (%)			Cancer detection rate (%)											
	NPB	PNB	PCD	All cancer				Gleason ≥7				Gleason 6			
	(*n* = 292)	(*n* = 172)	(*n* = 137)	NPB	PNB	PCD	*p* value	NPB	PNB	PCD	*p* value	NPB	PNB	PCD	*p* value
2	82 (28)	54 (31)	35 (26)	23.2	18.5	31.4	0.372	3.7	5.6	5.7	0.832	19.5	13.0	25.7	0.311
3	92 (32)	60 (35)	44 (32)	39.1	16.7	75.0	<0.001	16.3	5.0	29.5	0.003	22.8	11.7	45.5	<0.001
4	63 (22)	40 (23)	41 (30)	74.6	42.5	87.8	<0.001	50.8	25.0	53.7	0.014	23.8	17.5	34.1	0.215
5	55 (19)	18 (10)	17 (12)	92.7	88.9	100.0	0.403	87.3	83.3	94.1	0.612	5.5	5.6	5.9	0.998

NPB = no prior biopsy; PNB = prior negative biopsy; PCD = prior cancer diagnosis.

men with no prior biopsy, a prior negative biopsy, and a prior cancer diagnosis, respectively.

3.4. Relationship between mSS and cancer detection rates

There was a significant trend for higher detection of GS ≥7 PCa with higher mSS for SB and MRF-TB (both $p < 0.001$). This trend was not observed for GS 6 PCa detection for either SB ($p = 0.752$) or MRF-TB ($p = 0.896$; Fig. 3). The overall cancer detection rate was similar among the groups for men with mSS 2 and 5, but varied significantly by biopsy indication among men with mSS 3 or 4 ($p < 0.001$; Table 3).

3.5. MRF-TB versus SB stratified by mSS

To evaluate cancer detection rates according to mSS, men were split into groups on the basis of low or equivocal suspicion (mSS 2 or 3) and high or very high suspicion (mSS 4 or 5). SB detected more GS 6 cancer than MRF-TB in both groups ($p < 0.001$). In 370 men with mSS 2 or 3, MRF-TB detected significantly fewer PCas overall compared to SB ($p = 0.001$) but was similar for detection of GS ≥7 PCa ($p = 0.230$). In 234 men with mSS 4 or 5 lesions, MRF-TB detected significantly more PCas overall ($p = 0.005$) and significantly more GS ≥7 PCas ($p < 0.001$) than SB (Supplementary Table 3).

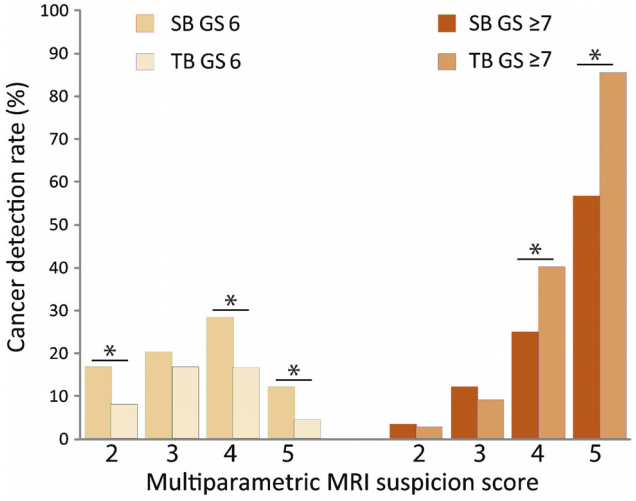

Fig. 3 – Cancer detection rate for systematic biopsy (SB) and magnetic resonance imaging-ultrasound fusion–targeted biopsy (TB) for GS 6 and GS ≥7 prostate cancer stratified by MRI suspicion score. * $p < 0.05$. GS = Gleason score; MRI = magnetic resonance imaging.

When evaluating the cohort by biopsy indication, for men with mSS 2 or 3 lesions, MRF-TB detected significantly fewer GS 6 PCas than SB alone in men with no prior biopsy ($p = 0.021$). There was no significant difference between MRF-TB or SB in detection of GS 6 or GS ≥7 PCa in men with a prior negative prostate biopsy or a prior cancer diagnosis. In men with mSS 4 or 5 lesions, MRF-TB detected significantly fewer GS 6 PCas than SB alone in men with no prior biopsy ($p = 0.002$), but was similar to SB in men with a prior negative biopsy ($p = 1.0$) or a prior cancer diagnosis ($p = 0.055$). However, MRF-TB detected more GS ≥7 PCa compared to SB in all three groups.

4. Discussion

Many recent studies have evaluated the outcome of MRF-TB compared to SB [11–14]. Although the detection rate has varied among studies, MRF-TB consistently detected more clinically significant cancers (median difference 6.8%) compared to SB, and found cancers (median 9.1%) missed by SB alone [15]. Our study findings compare favorably with previous series evaluating the relative performance of MRF-TB and SB in men with mixed indications for biopsy [13,14,16]. In the largest study, Siddiqui et al [14] demonstrated greater detection of GS ≥ 4 + 3 PCa using a transrectal fusion system compared to SB (17.2% vs 12.2%) in a cohort of 1003 men, largely comprised of men with a previous biopsy. Although our analysis was designed to answer questions similar to those addressed in previous studies, our study is distinct in that our cohort does not reflect a group of men referred for MRI-based risk assessment and biopsy, but rather reflect a consecutive cohort of men presenting for prostate biopsy based on clinical indications. All men underwent prebiopsy MRI and then targeted sampling if the MRI results were abnormal. The primary effect of this distinction is that a much larger proportion of our cohort is comprised of men without a prior biopsy in comparison to the cohort of Siddiqui et al (49% vs 20%) [14].

In addition, rather than focusing on the general outcomes of targeted biopsy, we chose to investigate the relationship between prebiopsy MRI findings and biopsy indication and biopsy outcome. Because it is likely that the performance characteristics of MRF-TB varied with the prevalence of disease in the study cohort, such an evaluation may allow insight into the optimal utilization of MRI-targeted biopsy in clinical practice. In men with no prior biopsy, MRF-TB identified more GS ≥7 cancers and

fewer GS 6 cancers than SB. This is probably because of identification of missed cancers and more accurate risk stratification. In men with a prior negative biopsy, MRF-TB identified more GS ≥7 cancers than SB, but overall detection of GS 6 cancers was relatively low with either technique, probably because of the previous sampling.

The relative contribution of SB to detection of high-grade cancer also varied by biopsy indication. Among men with no prior biopsy, 10/98 (10.2%) with GS ≥7 cancer were diagnosed solely by SB. Similarly, among men with a previous biopsy positive for GS 6 cancer, upgrading to GS≥ 7 on SB alone was noted in 11/53 (20.8%). These findings may in part reflect the relative prevalence of GS ≥7 cancer in each group, errors in biopsy targeting, or qualitative differences (such as tumor volume and relative high-grade component) in the cancers missed compared to those found by MRF-TB. Regardless of the reason, the greatest potential to reduce overdetection of indolent disease would be through avoidance of SB, particularly in men with no previous biopsy, but this may come at the cost of missing some high-grade cancers. By contrast, among men with a previous negative biopsy, SB did not uniquely identify any men with GS ≥7 cancer in whom no cancer was found on MRF-TB. For these men, avoidance of SB would seem prudent, but given the small number of low-grade cancers found, the impact on reducing overdetection may be relatively small.

In evaluating the outcomes for men undergoing MRF-TB after prebiopsy mpMRI, several important observations regarding the relationship between mSS and biopsy findings can be made. First, there is a positive trend between increasing mSS and detection of high-grade (GS ≥7 PCa) disease, but not detection of GS 6 disease, on MRF-TB or SB. This demonstrates the selective nature of prebiopsy mpMRI in identifying high-grade disease, and the potential for its use in selecting men who would most benefit from MRF-TB. In addition, a low mSS may be useful in predicting low likelihood of high-grade PCa, so a biopsy could potentially be avoided. For example, if none of the 171 men with mSS 2 in our series were biopsied, only eight cancers with GS 3 + 4 and none with GS ≥ 4 + 3 would have been missed, while detection of 31 GS 3 + 3 cancers would have been avoided. Finally, the likelihood of cancer detection for each mSS level varies by biopsy indication, probably because of the prevalence of disease in each group. This has been demonstrated for men undergoing MRI-guided biopsy [17], and our data suggest that the greatest variation in cancer detection by biopsy indication is among men with intermediate mSS of 3 or 4 (Table 3).

Our findings collectively suggest that combining mSS and biopsy indications may help in identifying men for whom prostate biopsy is unlikely to detect significant disease. A reduction in biopsy utilization and limitation of indolent cancer detection offer the potential to partially offset the cost of prebiopsy mpMRI by reducing the costs incurred for biopsy, treatment, and secondary complications. Any such reductions will rely on future standardization of MRI interpretation and MRI acquisition protocols. In addition, the initial risk-stratification biopsy upgrade rate of 39% using a combination of MRF-TB and SB for men with a prior cancer diagnosis is higher than the upgrade rate of 15–30% reported for confirmatory or first surveillance prostate biopsy [18–20]. Using a single biopsy, we achieved similar upgrade rates to those for men on active surveillance undergoing serial biopsies over many years [19,21]. Given its more accurate risk stratification, MRF-TB may potentially save patients from undergoing multiple rounds of repeat risk stratification biopsy without significant numbers of missed high-grade cancers.

Our study is limited by its retrospective in nature, so it suffers from potential for selection biases related to the nature of our institutional referral practice. In addition, our reference standard remains a biopsy rather than a final prostatectomy specimen, so we cannot validate our scoring accuracy and determine the actual significance of a negative biopsy. Our analysis excluded men without visible lesions on mpMRI, so we could not assess the rate of significant cancer in such men. In addition, we did not correct for multiple comparisons. Finally, clinical recommendations derived from our data must be predicated on our considerable experience with mpMRI of the prostate, its interpretation, and MRI-targeted biopsy techniques. Whether such observations could be duplicated in other centers remains to be determined through additional studies.

Despite its limitations, our study has several strengths, including the fact that all men presenting to our center during the study period underwent prebiopsy mpMRI when medically feasible, which reduced the likelihood of selection bias to some extent. While the PROFUS study conducted at our institution [5] found no difference in co-registration–guided and cognitive-directed MRI targeting, we have adopted MRF-TB as our standard biopsy approach since March 2013 (end of PROFUS accrual) given the ability to standardize the biopsy approach, reduce the operator learning curve, reduce intraoperator variability, and provide standard methods for computer-directed 12-core biopsy. Owing to the standardized MRI interpretation and biopsy protocols using an automated system, operator variability in the biopsy technique is also reduced. While our reference standard remains biopsy, the analysis does offer the opportunity to compare biopsy techniques and outcomes that ultimately drive clinical management. Our findings can inform the design of future prospective studies of MRI-based risk stratification.

5. Conclusions

MRF-TB detects more GS ≥7 cancers compared to SB while limiting the detection of indolent disease in all men presenting for prostate biopsy. Higher mSS values correlate strongly with a higher likelihood of GS ≥7 cancer in all men, regardless of biopsy indication. The role of prebiopsy mpMRI, prediction of cancer risk, the need for SB, and the performance characteristics of MRF-TB all vary greatly by biopsy indication and mSS. While the clinical impact and benefit of MRF-TB vary by biopsy indication, the technique does seem to offer clear clinical benefit in all groups. Our data provide a framework for the design of further trials to evaluate MRI-targeted biopsy. Our results also strongly

suggest that prebiopsy mpMRI and MRF-TB should be considered in all men undergoing prostate biopsy.

Author contributions: Samir S. Taneja had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Taneja, Rosenkrantz, Meng, Mendhiratta.
Acquisition of data: Meng, Rosenkrantz, Mendhiratta, Wysock, Fenstermaker, Huang, Bjurlin, Marshall, Deng, Melamed, Zhou, Huang, Lepor, Taneja.
Analysis and interpretation of data: Meng, Mendhiratta, Rosenkrantz, Taneja.
Drafting of the manuscript: Meng, Mendhiratta, Taneja.
Critical revision of the manuscript for important intellectual content: Meng, Rosenkrantz, Wysock, Bjurlin, Marshall, Deng, Melamed, Zhou, Huang, Lepor, Taneja.
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Appendix A. Supplementary data

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