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Pre-Biopsy MRI and MRI-Ultrasound Fusion-Targeted Prostate Biopsy in Men with Previous Negative Biopsies: Impact on Repeat Biopsy Strategies

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Abstract

OBJECTIVE—To report outcomes of MRI-ultrasound fusion (MRF-TB) and 12-core systematic biopsy (SB) over a 26-month period in men with prior negative prostate biopsy.

METHODS—Between 6/12 and 8/14, 210 men presenting to our institution for prostate biopsy with 1 prior negative biopsy underwent multiparametric MRI followed by MRF-TB and SB and were entered into a prospective database. Clinical characteristics, MRI suspicion scores (mSS), and biopsy results were queried from the database and the detection rates of Gleason 7 prostate cancer (PCa) and overall PCa were compared between biopsy techniques using McNemar's test.

RESULTS—Fifty-three (31%) of 172 men meeting inclusion criteria (mean age 65±8 years; mean PSA 8.9±8.9) were found to have PCa. MRF-TB and SB had overall cancer detection rates (CDR) of 23.8% and 18.0% (p=0.12), respectively, and CDR for Gleason score (GS) 7 disease of 16.3% and 9.3% (p=0.01), respectively. Of 31 men with GS 7 disease, MRF-TB detected 28 (90.3%) while SB detected 16 (51.6%) (p<0.001). Using UCSF-CAPRA criteria, only one man was re-stratified from low-risk to higher risk based on SB results compared to MRF-TB alone. Among men with mSS<4, 80% of detected cancers were low-risk by UCSF-CAPRA criteria.

CONCLUSIONS—In men with previous negative biopsies and persistent suspicion for PCa, SB contributes little to the detection of GS 7 disease by MRF-TB, and avoidance of SB bears

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consideration. Based on the low likelihood of detecting GS 7 cancer and overall low-risk features of PCa in men with mSS<4, limiting biopsy to men with mSS ≥ 4 warrants further investigation.

Keywords

prostate MRI; MRI-US fusion; prostate biopsy; prostate cancer; repeat biopsy

INTRODUCTION

Approximately 1 in 5 men treated surgically for prostate cancer (PCa) undergoes multiple prostate biopsies before being diagnosed with cancer^{1,2}. Recent evidence demonstrates that men with negative primary prostate biopsy often undergo repeat biopsy, with up to 25% cancer detection even after the 4th repeat biopsy^{3,4}. Multiple repeat biopsies increase cost, delay diagnosis, and risk unnecessary morbidity, all of which would improve with more accurate biopsy.

Recent investigations into image-guided prostate biopsy using multiparametric MRI (mpMRI) have demonstrated the superior ability of MRI-targeted biopsy to detect clinically significant cancers missed by systematic biopsy^{5,6}. However, the performance of targeted biopsy in improving high-risk cancer detection, as well as reducing over-detection of low-risk disease, is influenced by the prevalence of cancer in the tested population, which varies widely with the clinical indication for biopsy and pre-biopsy characteristics⁷. Men with prior negative biopsies and persistent suspicion of prostate cancer represent a population with a relatively low prevalence of disease due to prior sampling. As such, pre-biopsy MRI may enhance detection of occult cancers by localization of disease in areas of the prostate undersampled by systematic biopsy. Additionally, pre-biopsy mpMRI may not only predict the likelihood and severity of occult disease, as previously reported^{8,9}, but may even provide further discriminating information so as to identify candidates who are least likely to benefit from prostate biopsy.

In this study, we report the overall cancer detection rates and high-grade cancer detection rates of MRI-US fusion targeted biopsy (MRF-TB) and 12-core systematic biopsy (SB) in men with previous negative biopsies and persistently elevated PSA. In an effort to define an optimal biopsy approach for these men, we further investigate the clinical impact of pre-biopsy characteristics, including mpMRI, in the ability to identify men who may derive maximal benefit from MRF-TB, minimal benefit from SB, and minimal benefit from prostate biopsy overall with respect to high-grade cancer detection.

MATERIALS & METHODS

Study design and population

Between June 2012 and August 2014, all men presenting to our institution for prostate biopsy were offered pre-biopsy mpMRI to identify areas within the prostate suspicious for cancer. 210 men with prior negative biopsies and areas of suspicion identified on mpMRI underwent MRF-TB and SB, and outcomes were recorded in an IRB-approved database. We retrospectively analyzed clinical characteristics, maximum mpMRI suspicion scores (mSS),

and biopsy results from men with at least one previous negative biopsy. Men were excluded if they had a history of prior MRF-TB (n=4), had undergone MRI at an outside institution or using nonstandard protocol (n=12), or had an incomplete record in our database (n=22). Clinical datapoints, such as biopsy indication, PSA, mSS, and biopsy outcomes were queried from the database.

Multiparametric MRI

mpMRI was performed using a 3T whole-body system and a pelvic phased-array coil and included multiplanar turbo-spin echo T2-weighted images (T2WI), axial single-shot echo-planar imaging diffusion-weighted imaging (DWI) with b-values of 50 and 1,000 sec/mm², and dynamic contrast-enhanced imaging (DCE) MRI following intravenous administration of gadolinium-chelate. Prior to biopsy, MRI studies were reviewed by a single fellowship-trained radiologist with 5–6 years of experience in prostate MRI at the time of this study, who identified suspicious foci within the prostate. The probability for tumor was scored on a 5-point Likert scale, as previously reported^{7,10,11}: mSS 2 (low probability), 3 (equivocal), 4 (high probability), or 5 (very high probability). Studies with no identified suspicious region received a score of 1 and were not candidates for MRI-targeted biopsy.

MRI-US fusion targeted biopsy

MRF-TB was performed using the Artemis/Pro-fuse™ (Eigen, Grass Valley) prostate biopsy system, as described in our previous work⁷. In brief, T2 sequences with delineated tumor boundaries were transferred to the Artemis system prior to biopsy. Computer-assisted coregistration of segmented MRI and US images of the prostate was performed using manual rigid translation followed by elastic deformation. Transrectal biopsies were obtained with the patient in left lateral decubitus position, beginning with 3–4 cores targeted to each suspicious lesion followed by 12 systematically distributed cores. The locations of the 12 systematic cores were automatically generated by the Artemis system, and not by the urologist. The procedure utilized the Pro Focus (BK Medical, Peabody, MA, USA) or Noblus ultrasound system (Hitachi Aloka Medical America, Wallingford, CT, USA), endfire probe, 18G needles, and local anesthesia with 1% lidocaine infiltration.

For each patient, systematic and targeted biopsies were performed by one of four faculty urologic oncologists, experienced in prostate biopsy. All biopsy cores were analyzed by one of three subspecialized genitourinary pathologists at our institution. Biopsy results were compared using the highest Gleason score (GS) obtained by each technique. Analysis of clinically significant cancer detection was done based on two definitions for clinical significance: GS ≥ 7 and primary Gleason grade 4 or higher (pGG ≥ 4). Analysis of clinically insignificant cancer detection was done based on Epstein¹² and UCSF-CAPRA¹³ (score ≥ 2) criteria.

Statistical analysis

Categorical variables, including a history of HGPIN and/or ASAP, median time since last biopsy, and percentage of positive biopsy cores were compared using the chi-square test. Normally distributed continuous variables were evaluated with the Student t-test. Comparison of cancer detection rates between SB and MRF-TB was assessed by

McNemar's test. All analysis was carried out in SPSS v.21.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 210 men with prior negative biopsies who underwent mpMRI followed by biopsy were identified, of whom 172 men met inclusion criteria, as above. Clinical characteristics are described in Table 1. The mean number of lesions and biopsy cores taken per prostate were 1.5 and 18.0, respectively.

Cancer detection: MRF-TB vs SB

Overall, cancer was identified in 53 (31%) men who underwent MRF-TB and SB. Although cancer detection rates (CDRs) were higher for MRF-TB than SB, this difference was not clinically significant (23.8% vs 18.0%, respectively, $p = 0.12$) (Table 2). Compared to SB, MRF-TB detected more GS 7 disease (90% vs 52%, $p < 0.01$) and more pGG 4 disease (94% vs 50%, $p = 0.02$). MRF-TB demonstrated improved sampling efficiency compared to SB, as a total of 126/1036 (12.2%) targeted cores and 67/2064 (3.2%) systematic cores identified PCa, and the mean number of cores required per diagnosis of GS 7 cancer was 37 and 129 on targeted and systematic biopsy, respectively.

While no men with GS 7 cancer detected by SB had negative MRF-TB, three GS (3+4) cancers identified by SB were mischaracterized as GS 6 by MRF-TB. Two of these cases demonstrated <10% pattern 4 disease in only one SB core. In the third case, GS 7 cancer was detected on the SB core adjacent to the area of the prostate with the targeted MRI lesion.

Compared to men with negative biopsies, men with positive MRF-TB or SB had no significant difference in the time elapsed since last standard transrectal biopsy ($p = 0.92$) or number of previous biopsies ($p = 0.72$). There was additionally no association between the number of previous biopsies and the probability of cancer detection by SB ($p = 0.38$) or MRF-TB ($p = 0.59$). Among 41 men with PCa detected by MRF-TB, 17 (41%) had PCa identified in the anterior prostate only, among whom SB yielded no cancer in 9/17 (53%).

Maximum mpMRI suspicion scores

mSS 2–5 were reported in 54 (31%), 60 (35%), 40 (23%), and 18 (10%) men, respectively. Men with mSS 4 lesions harbored the majority of GS 7 and pGG 4 cancers detected (25/31 (81%) and 18/18 (100%), respectively). In men with mSS 4 lesions, MRF-TB detected all 25 GS 7 cancers, while SB missed 12/25 (48%) ($p = 0.001$) (Figure 1).

mSS < 4 had a negative predictive value (NPV) of 95% and 100% for GS 7 and pGG 4 disease, respectively. Of all cancers detected in men with mSS < 4 lesions, most were clinically insignificant by Epstein (60%) and UCSF-CAPRA (80%) criteria, respectively. Of all GS 7 cancers found in men with mSS < 4, 83% demonstrated GS 7(3+4) cancer in only one core with 10% Gleason pattern 4, and 50% demonstrated UCSF-CAPRA score 2 (Table 3). Only 1/114 (0.9%) men with mSS < 4 was found to have GS 7(3+4) in multiple cores, and none were found to have pGG 4 PCa.

DISCUSSION

The management of men with previous negative biopsy, and persistent clinical suspicion of PCa, remains a challenging task for the practicing urologist. In addition to the absence of consensus guidelines regarding the indication for repeat biopsy, the optimal approach to such patients when biopsy is indicated is unclear. We have previously shown that men with persistent suspicion for cancer often undergo repetitive cycles of biopsy before diagnosis⁴. Prior studies have explored the potential for MRI-targeted biopsy to better detect cancers than systematic biopsy among men with prior negative biopsies and, in doing so, reducing the need for multiple subsequent biopsies and delays in diagnosis^{14–16}. In this paper, we aimed to expand on these findings and provide data to shape a clinical paradigm for this population, specifically by evaluating the characteristics of cancers missed by targeted biopsy and by exploring the relationship between pre-biopsy MRI and the likelihood of cancer on biopsy. Our data suggests not only that avoidance of systematic biopsy, which has minimal contribution to the detection of high grade cancer, may be considered, but also that pre-biopsy MRI may allow identification of men with prior negative biopsies who have a low likelihood of high-grade disease and who may not benefit from repeat biopsy at all. Until a time when the implementation of MRI-targeted biopsy in clinical practice is clearly defined and accepted, we feel there is a tremendous need for data supportive of, or refuting, the paradigm.

In a recent report of 1003 men undergoing MRF-TB by Siddiqui et al¹⁷, among whom 43% had prior negative biopsies, the investigators demonstrated a 30% improvement in high-grade cancer detection with MRF-TB compared to SB, though 15% of men demonstrated a higher risk category with SB compared to MRF-TB. In our study, the overall contribution of SB to MRF-TB results was limited. Among the few men with GS 7 disease detected by SB and missed or mischaracterized by MRF-TB, most had low-volume disease, and only one was classified as higher risk by SB compared to MRF-TB using UCSF-CAPRA criteria. Additionally, SB made no contribution to the detection of GS 7 cancer in men with MRI abnormalities of mSS 4. Collectively, as suggested in prior series¹⁶, these findings indicate that SB has minimal impact on detection of high-grade cancer and risk stratification among men with prior negative sampling, and thus may be of little value in combination with MRF-TB.

One potential reason why MRF-TB was superior to SB in detecting PCa may be that over 40% cancers identified by MRF-TB were found in the anterior prostate. While it has been proposed that transperineal template biopsy may be an option for men with previous negative biopsies due to improved access to the anterior prostate, current evidence suggests that MRI-targeted biopsy has a comparable detection rate of clinically significant cancers while reducing over-detection of clinically insignificant disease as compared to transperineal template biopsy^{18–20}.

Ultimately the likelihood of high grade cancer detection was strongly predicted by mSS. Previous studies have similarly demonstrated a strong association between suspicion of cancer based on mpMRI and cancer detection^{16,21,22}. Salami et al.¹⁶ recently reported outcomes of a prospective trial comparing MRF-TB to SB in 140 men with prior negative

biopsies. They demonstrated a strong association between increasing MRI suspicion score and CDR of both MRF-TB and SB. Their reported overall CDR of 65.0% is higher than that found in our series, though this is likely due in part to a lower proportion of their cohort with low suspicion lesions (mSS 2 in 6% vs 31%). Sonn et al²³ reported a series of 105 men with previous negative biopsy who underwent MRF-TB and SB and demonstrated that lesions with suspicion scores of 2, 3, 4 and 5 corresponding to 6%, 4%, 21%, and 75% detection of clinically significant PCa, respectively.

Our results specifically suggest that abnormalities of mSS 2 and 3 predict a very low likelihood of cancer overall, and an even lower likelihood of high grade disease. Electing to forego any biopsy in the 114 men with low probability or equivocal lesions would have avoided detection of clinically indolent cancers in 12 to 14 men (depending on the definition utilized), while missing GS 7 (3+4) cancers in 6 (5%) men and GS 7 (4+3) or higher grade cancers in no men. Three of the six GS 7 cancers may have been considered low risk based upon further analysis as previously discussed. These findings suggest that cancers identified in men with previous negative biopsies and low to equivocal MRI-suspicion scores are largely low risk. As such, pre-biopsy mpMRI may have the potential to identify men within this population who may be able to safely avoid repeat biopsy due to a low likelihood of significant disease.

Strengths of this study protocol include the fact that all men presenting to our center for consideration of repeat biopsy were recommended pre-biopsy mpMRI, MRI suspicion grading was carried out by a single radiologist, and our biopsy approach with software co-registration was standardized among 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. As a result, indications for biopsy in the population of men receiving MRI were not ascertained. Additionally, not all men with normal MRI (mSS 1) were recommended biopsy since they had undergone one or more recent SB prior to presentation. Another potential limitation is the use of Epstein and UCSF-CAPRA criteria for the assessment of clinically insignificant cancers, which, while conservative and not yet validated in targeted biopsy, may be the best available measure to estimate the proportion of indolent disease. Finally, as many men underwent previous biopsies outside of our institution, the technique of previous biopsy and the pathologic interpretation of such biopsies were not standardized. Nonetheless, we believe the study provides important insight into the conduct of biopsy in men with previous negative sampling, and provides additional supportive data for the use of pre-biopsy mpMRI in this group of men.

CONCLUSIONS

In men with one or more previous negative biopsies, and persistent suspicion for PCa, the use of pre-biopsy mpMRI followed by MRF-TB provides greater overall and clinically significant cancer detection than SB alone. The marginal contribution of SB to the detection of clinically significant cancer suggests that MRF-TB alone may be a sufficient biopsy strategy in this cohort, especially in men with mSS \geq 4. Among men with mSS $<$ 4, the low rate of GS 7 PCa detection as well as overall low-risk features of all detected PCA may warrant consideration of avoiding biopsy in these men. Further prospective studies

comparing MRF-TB and SB in men with previous negative biopsy, along with community-based standardization of prostate mpMRI acquisition and interpretation, are needed prior to widespread implementation of the approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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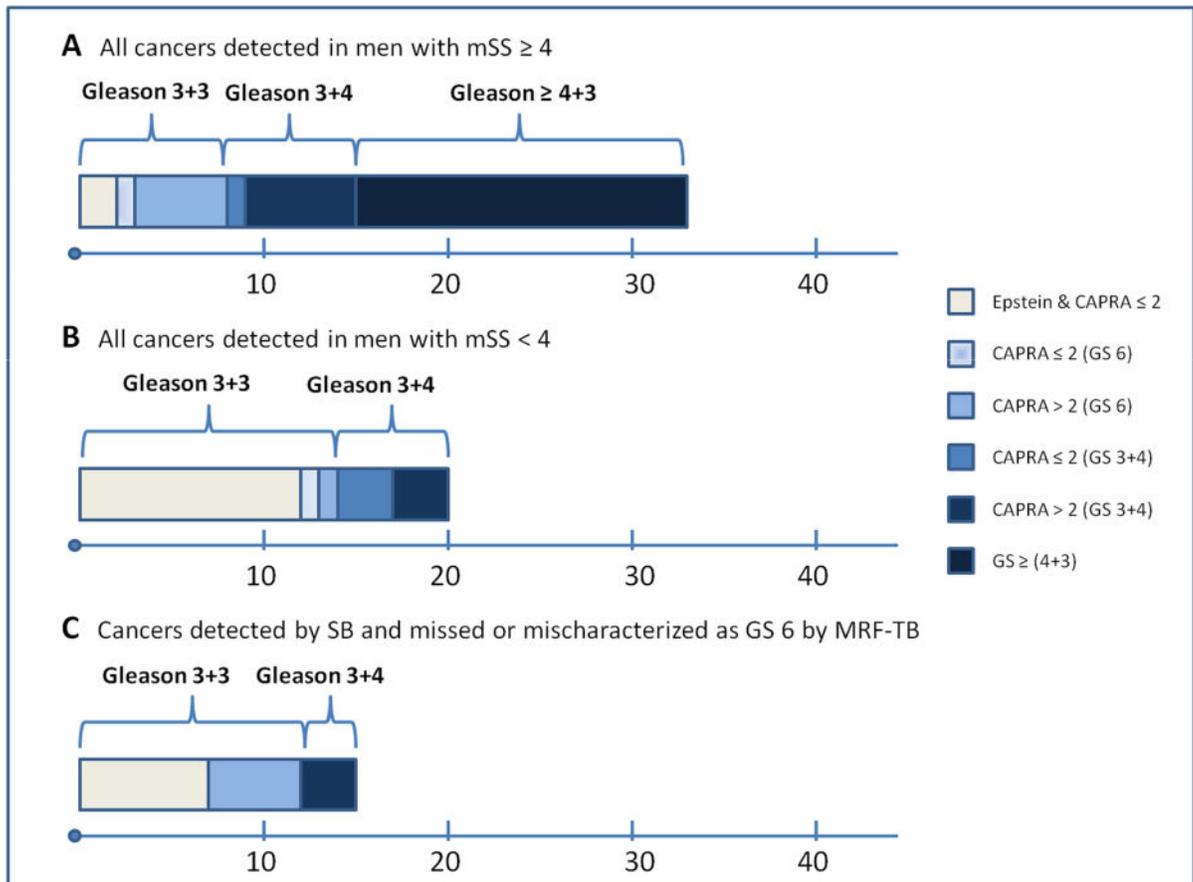


Figure 1.

Grade distribution of detected prostate cancers showing the number of men (x-axis) with the indicated prostate cancer grade among (a) men with mSS ≥ 4 , (b) men with mSS < 4 , and (c) men with cancer on SB which was missed or mischaracterized as Gleason 6 by MRF-TB.

Patient characteristics

Table 1

	Total n = 172	Results of MRF-TB and SB		p-value	Results of MRF-TB and SB		p-value
		Cancer n = 53 (30.8%)	No cancer n = 119 (69.2%)		GS 7 Cancer n = 31 (18.0%)	GS 6 or no cancer n = 141 (82.0%)	
Age (mean, years)	65.1 ± 7.6	66.8 ± 7.9	64.4 ± 7.4	0.056 [†]	65.6 ± 8.2	64.6 ± 9.3	0.583 [†]
PSA (mean [SEM], ng/mL)	8.9 [0.7]	11.6 [1.4]	7.7 [0.7]	0.017[†]	14.9 [2.1]	7.6 [0.6]	<0.001[†]
Number of previous biopsies (mean)	2.2	2.13	2.23	0.723 [†]	2.4	2.2	0.555 [†]
MRI Prostate volume (mean [SEM], cc)	72.5 [3.22]	69.1 [6.6]	74.0 [3.7]	0.485 [†]	68.1 [9.3]	73.5 [3.3]	0.515 [†]
Time since last biopsy (median, mo.)	31.4	31.2	31.4	0.920 [*]	23.0	32.6	0.448 [*]
Previous HGPIN/ASAP							
HGPIN or ASAP	53 (30.8%)	16 (30.2%)	37 (31.1%)	0.906 [*]	9 (29.0%)	44 (31.2%)	0.812 [*]
HGPIN	43 (25.0%)	11 (20.8%)	32 (26.9%)	0.391 [*]	4 (12.9%)	39 (27.7%)	0.086 [*]
ASAP	26 (15.1%)	12 (22.6%)	14 (11.8%)	0.066 [*]	9 (29.0%)	17 (12.1%)	0.017[*]
HGPIN and ASAP	16 (9.3%)	7 (13.2%)	9 (7.6%)	0.239 [*]	4 (12.9%)	12 (8.5%)	0.362 [*]
mSS distribution				< 0.001^{**}			< 0.001^{**}
mSS 2	54 (31.4%)	9 (17.0%)	45 (37.8%)		3 (9.7%)	51 (36.2%)	
mSS 3	60 (34.9%)	11 (20.8%)	49 (41.2%)		3 (9.7%)	57 (40.4%)	
mSS 4	40 (23.3%)	17 (32.1%)	23 (19.3%)		10 (32.3%)	30 (21.3%)	
mSS 5	18 (10.5%)	16 (30.2%)	2 (1.7%)		15 (48.4%)	3 (2.1%)	

GS: Gleason score

mSS: maximum MRI suspicion score

[†] Student t-test

^{*} Chi-square test for independence

^{**} Wilcoxon rank-sum analysis

Table 2

Cancer detection rates: MRF-TB vs SB

		MRI-Targeted Biopsy, n (%)			Total
		Gleason 7	Gleason 6	No cancer	
Systematic Biopsy, n (%)	Gleason 7	13 (8%)	3 (2%)	0 (0%) *	16 (9%) *
	Gleason 6	1 (1%)	2 (1%)	12 (7%)	15 (9%)
	No Cancer	14 (8%)	8 (5%)	119 (69%)	141 (82%)
	Total	28 (16%) *	13 (8%)	131 (77%)	172 (100%)

* p < 0.01

Table 3

Characteristics of detected PCa

All PCa	Men with mSS ≥ 4 (n = 33)	Men with mSS < 4 (n = 20)	SB positive, MRF-TB negative or GS6 (n = 15)
Maximum Gleason score			
6 (3+3)	8 (24%)	14 (70%)	12 (80%)
7 (3+4)	7 (21%)	6 (30%)	3 (20%)
7 (4+3)	18 (55%)	0 (0%)	0 (0%)
Clinically insignificant cancers			
Epstein ¹⁰ criteria	2 (6%)	12 (60%)	7 (47%)
UCSF-CAPRA ¹¹ score ≥ 2	4 (12%)	14 (80%)	7 (47%)
Gleason ≥ 7 PCa	(n = 25)	(n = 6)	(n = 3)
Number of cores with pattern 4 disease			
1	6 (24%)	5 (83%)	2 (66%)
2	4 (16%)	0 (0%)	0 (0%)
3	15 (60%)	1 (17%)	1 (33%)
Involvement of pattern 4 disease (max)			
10%	4 (16%)	5 (83%)	2 (66%)
10–50%	2 (8%)	1 (17%)	1 (33%)
50%	18 (72%)	0 (0%)	0 (0%)
Not reported	1 (4%)	0 (0%)	0 (0%)
Maximum cancer core length			
2mm	3 (12%)	3 (50%)	1 (33%)
2mm to 4mm	2 (8%)	1 (17%)	1 (33%)
4mm	19 (76%)	1 (17%)	1 (33%)
Fragmented	1 (4%)	1 (17%)	0 (0%)
Clinically insignificant cancers			
UCSF-CAPRA ¹¹ score ≥ 2	1 (4%)	3 (50%)	0* (0%)

mSS: maximum MRI suspicion score

* All 3 GS 7 cancers detected by SB also demonstrated UCSF-CAPRA score > 2 based on MRF-TB alone.