Assessment of magnetic resonance imaging (MRI)-fusion prostate biopsy with concurrent standard systematic ultrasound-guided biopsy among men requiring repeat biopsy

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Cite as: Sun R, Fast A, Kirkpatrick I, et al. Assessment of magnetic resonance imaging (MRI)-fusion prostate biopsy with concurrent standard systematic ultrasound-guided biopsy among men requiring repeat biopsy. *Can Urol Assoc J* 2021;15(9):E495-500. http://dx.doi.org/10.5489/cuaj.6991

Published online February 12, 2021

Abstract

Introduction: The role of magnetic resonance imaging (MRI)-fusion biopsy (FB) remains unclear in men with prior negative prostate biopsies. This study aimed to compare the diagnostic accuracy of FB with concurrent systematic biopsy (SB) in patients requiring repeat prostate biopsies.

Methods: Patients with previous negative prostate biopsies requiring repeat biopsies were included. Those without suspicious lesions (≥Prostate Imaging-Reporting and Data System [PI-RADS] 3) on MRI were excluded. All patients underwent FB followed by SB. The primary outcome was the sensitivity for clinically significant prostate cancer (Gleason score ≥7). The secondary objective was identification of potential predictive factors of biopsy performance.

Results: A total of 53 patients were included; 41 (77%) patients were found to have clinically significant prostate cancer. FB had a higher detection rate of significant cancer compared to SB (85% vs. 76%, respectively, p=0.20) and lower diagnosis of indolent (Gleason score 3+3=6) cancer (10% vs. 27%, respectively, p=0.05). FB alone missed six (15%) clinically significant cancers, compared to 10 (24%) with SB. SB performance was significantly impaired in patients with anterior lesions and high prostate volumes (p<0.05). There was high degree of pathological discordance between the two approaches, with concordance seen in only 34% of patients.

Conclusions: In patients with prior negative biopsies and ongoing suspicion for prostate cancer, a combined approach of FB with SB is needed for optimal detection and risk classification of clinically significant disease. Anterior tumors and large prostates were significant predictors of poor SB performance and an MRI-fusion alone approach in these settings could be considered.

Introduction

Prostate cancer remains one of the most common causes of cancer mortality among males.[1] The current standard for diagnosis in men suspected to have prostate cancer involves a transrectal ultrasound-guided (TRUS) prostate biopsy, which uses a systematic approach to sample representative areas of the entire gland.[2,3] While this approach has a detection rate from 27–44%,[4] it is imperfect, with multiple shortcomings such as over-detection of clinically insignificant cancer and inaccuracy due to its non-targeting nature.

Magnetic resonance imaging (MRI) has emerged as a useful tool in the diagnostic pathway for prostate cancer.[5,6] Multiparametric prostate MRI allows delineation of suspicious lesions, which is especially useful in evaluating anterior regions of the prostate not typically sampled by a standard systematic TRUS biopsy (SB).[7,8] It also potentially detects higher-risk cancer and overlooks low-risk disease,[9] particularly in the setting of active surveillance.[10,11] More recently, MRI has been further incorporated via MRI-fusion biopsy (FB), which allows accurate sampling of suspicious lesions. MRI FB has since been shown to improve the detection rate of clinically significant cancer and has been adopted in routine practice and proposed as a new upfront biopsy technique.[12-14]

Despite encouraging evidence in the usefulness of MRI-FB, its role is not fully defined in men who had previously negative TRUS biopsies but have ongoing clinical suspicion for prostate cancer. Traditionally, these men would undergo a repeat TRUS biopsy, which may again be limited by inaccuracies of its non-targeted approach,[15] unlike MRI-FB that allows for accurate lesion-targeted sampling. To date, there is limited direct comparison between TRUS and FB specifically in this clinical scenario. In this study, we aim to compare the diagnostic accuracy between MRI-FB and concurrent TRUS systematic biopsies in men who require repeat biopsies, as well as to identify potential predictors of cancer detection in both techniques.

Methods

Patient selection

Institutional review board approval was obtained from the University of Manitoba Research Ethics Board (REB #HS22846). Consecutive patients with previously negative TRUS biopsies and who required repeat biopsies due to clinical suspicion of disease (persistently rising prostates-specific antigen [PSA], abnormal exams) from June 2017 to September 2018 were included in this single-center study. Patients with negative MRI findings, defined as no abnormal lesions or lesions of Prostate Imaging-Reporting and Data System (PI-RADS) <3, were excluded.

Imaging

All patients underwent MRI at a single radiology center. The patients were instructed to follow a low-residue diet prior to the study to reduce bowel gas and stool in the rectum. Multiparametric prostate imaging was performed using a 3 Tesla magnet (Siemens Verio, Siemens Healthineers, Erlangen, Germany) and a pelvic phased array coil, which included axial T1 and triplanar high-resolution T2-weighted turbo spin echo images, diffusion imaging (including directly acquired b-1500 images and ADC map generation), and dynamic perfusion imaging. Target lesions were identified by five fellowship-trained uro-radiologists with 5–17 years of prostate MRI experience at a high-volume radiology center (minimum 30 prostate MRIs per week). Each lesion was scored according to PI-RADS version 2.[16] Prostate volume, lesion size, and lesion location were documented. 3D contouring model of the prostate was then created by a single experienced radiologist using the Focal Fusion 3D workstation for use in subsequent MR fusion biopsy.

Combined software MRI-fusion and systematic TRUS biopsy

All patients with PI-RADS ≥3 lesions underwent concurrent MR-fusion and standard TRUS biopsies in one session, first with fusion biopsies performed with the Focal Fusion biopsy system and software (Focal Healthcare, Toronto, Canada). Both biopsies were performed by one of two experienced urologists under antibiotic prophylaxis. Local anesthesia was performed with lidocaine periprostatic block. Both techniques were performed transrectally using a 3D triplane transrectal ultrasound system (BK Medical, Herlev, Denmark). Three to four cores were obtained for each prostate lesion scoring ≥PI-RADS 3. The standard TRUS biopsy was then performed systematically, taking 12 cores in total to acquire sampling from medial and lateral aspects of each sextant prostate region as per international standards.[17] All biopsy samples were reported by expert uro-pathologists blinded to MRI and clinical findings.

Statistical analysis

Data analysis was performed to summarize clinical, radiographical, and biopsy characteristics. Chi-squared, Student's t-test, and ANOVA were used to evaluate association between different parameters and the detection of clinically significant prostate cancer, defined as any Gleason score ≥7. Tests were two-sided and considered statistically significant if $p<0.05$. Statistical analysis was performed using SPSS version 20.

Results

A total of 53 men and 68 lesions were included in this study. All 53 underwent simultaneous MRI-guided and systematic TRUS biopsies. Forty-one patients (77%) were found to have clinically significant prostate cancer, despite previous negative TRUS biopsies. Table 1 summarizes clinical and radiographical characteristics of patients with and without cancer. Abnormal digital rectal exam and higher PI-RADS scores were associated with detection of clinically significant cancer ($p<0.05$).

The performance of FB compared to standard SB is summarized in Table 2. FB detected 35 of 41 (85%) patients with clinically significant prostate cancer, while SB detected 30 of 41 (74%), which was not significantly different ($p=0.20$). Both approaches missed detection of significant disease; 6/41 (15%) of such cases were missed by FB, and 11/41 (27%) by SB. Thirteen patients were found to have low-risk (Gleason score=6) disease, 11 (85%) of which were detected by SB, while only four (13%) were detected by FB ($p=0.05$). FB was shown to better detect clinically significant disease

Table 1. Clinical and radiographic parameters in patients with and without prostate cancer

	All patients (N=53)	No csPCa (n=12)	csPCa (n=41)	p
Age (year ± SD)	66.0±8.0	62.7±6.9	67.0±8.1	0.10
DRE positive (%)	14/46 (30%)	1/11 (9%)	13/35 (37%)	0.030
PSA at biopsy (ng/ml)	11.3±10.0	10.4±6.9	11.6±10.7	0.74
Prostate volume (ml)	44.3±22.4	49.6±27	42.4±22	0.37
PSA density (ng/ml^2)	0.27±0.31	0.18±0.17	0.31±0.34	0.31
PI-RADS score (%)				0.027
3	14/53 (26%)	7/12 (58%)	7/41 (18%)	
4	19/53 (36%)	2/12 (17%)	17/41 (41%)	
5	20/53 (41%)	3/12 (25%)	17/41 (41%)	
Lesion size (mm ± SD)	14.5±8.0	14.1±7.0	16.0±8.6	0.53

csPCa: clinically significant prostate cancer; DRE: digital rectal examination; PI-RADS: Prostate Imaging-Reporting and Data System; PSA: prostate-specific antigen; SD: standard deviation.

Table 2. Biopsy characteristics

	Fusion biopsy	Systemic biopsy	p
Sensitivity of csPCa	35/41 (85%)	31/41 (76%)	0.20
Number of csPCa missed	6/41 (15%)	10/41 (24%)	
Detection of low-risk PCa	4/13 (31%)	11/13 (85%)	0.05
Sensitivity of csPCa if anterior lesions	16/22 (70%)	8/22 (35%)	<0.01
Positive Bx, by lesion size			
<10 mm	10/21 (48%)	10/15 (67%)	0.43
10–20 mm	12/24 (50%)	14/18 (78%)	0.54
>20 mm	11/13 (85%)	10/12 (83%)	0.17
p	0.21	0.97	
Positive biopsy by PI-RADS score			
3	7/17 (41%)	5/14 (36%)	1.00
4	14/28 (50%)	13/19 (68%)	0.13
5	17/21 (81%)	12/20 (60%)	1.00
p	0.01	0.39	
Positive biopsy, by prostate volume (ml)			
<30	3/5 (60%)	3/5 (60%)	1.00
30–50	10/16 (63%)	12/16 (75%)	0.19
50–100	9/11 (82%)	6/11 (55%)	0.34
>100	1/4 (25%)	0/4 (0%)	0.42
p	0.26	0.046	

Bx: biopsy; csPCa: clinically significant prostate cancer; PI-RADS: Prostate Imaging-Reporting and Data System.

among the 22 patients with anterior lesions on MRI in comparison to SB (16 [70%] vs. 8 [(35%)], respectively, p<0.01).

Lesion size, as seen on MRI, was not predictive of disease detection. Increasing PI-RADS score was predictive of positive FB (p=0.05) but not for SB (p=0.88). Increasing prostate volume was associated with negative SB (p=0.046) but did not seem to affect FB (p=0.26). Lesion location within the posterior prostate, stratified into four anatomical zones (right lateral, right medial, left lateral, and left medial), did not predict or differ in detection of significant disease with either FB or SB (Fig. 1). In contrast, lesions located within the anterior gland predicted poor detection rate by SB (p<0.01).

Using the same four-zone designation, 22 (54%) of the patients with clinically significant disease were detected by SB from cores corresponding to the zones in which the lesions were located based on MRI. Eight (20%) of these patients were detected by SB to harbor significant disease in areas deemed normal by the initial MRI (Fig. 2).

In two cases (4.9%), the cancer detected was found in the side contralateral to the MRI-identified lesion.

Table 3 depicts the concordance of pathology results between FB and SB. Eighteen patients (34%) had exact pathological concordance in Gleason scores, while 15 patients (28%) had upgrade in Gleason scores with FB and 20 patients (38%) had an upgrade with SB as compared to the counterpart biopsy method. Four patients (7.5%) were diagnosed with clinically significant prostate cancer

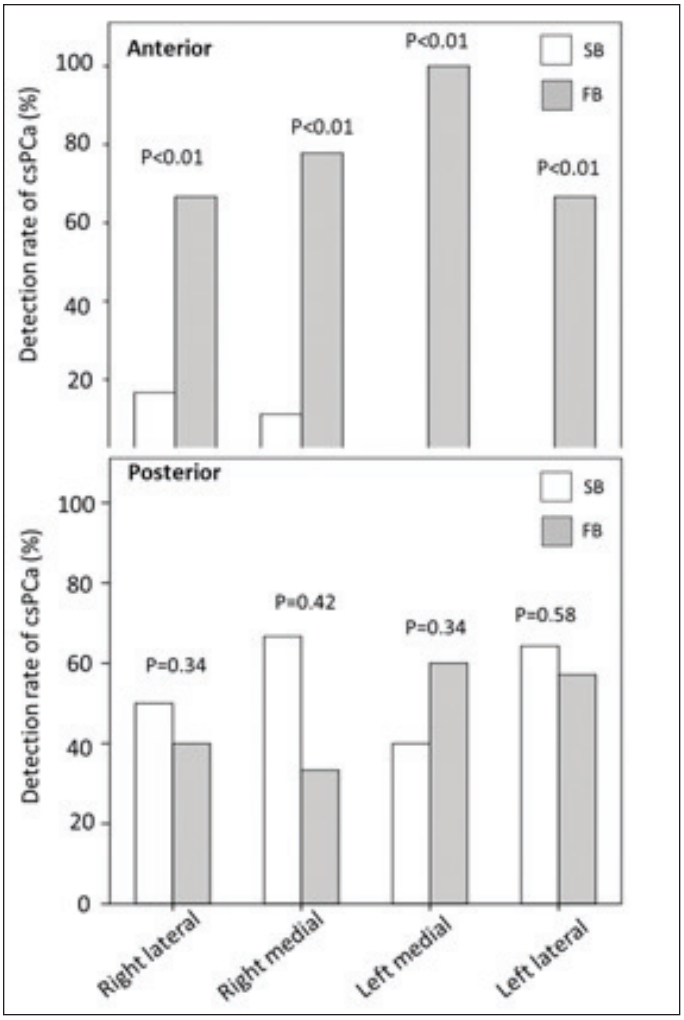

Fig. 1. Comparison of clinically significant prostate cancer (csPCa) detection rate between systematic (SB) and fusion (FB) biopsy based on lesion location. Patients with anteriorly located lesions were better diagnosed by FB, while those with posteriorly located lesions were similarly diagnosed by both FB and SB. There was no general difference in detection rate between different zones of prostate gland (p<0.05).

on FB, with the repeat SB returning benign results, while three patients (5.7%) were diagnosed by SB with negative FB results.

Concurrent use of FB and SB was well-tolerated, resulting in only two (3.8%) complications in this cohort. There was one instance of mildly increased intraprocedural hemorrhage and one instance of a postoperative infection due to an organism resistant to prophylactic antibiotics. Both complications were resolved on followup without issue.

Discussion

MRI-guided FB has emerged as a promising technique for prostate cancer detection, allowing direct targeting of suspicious lesions rather than systematic sampling. Validation

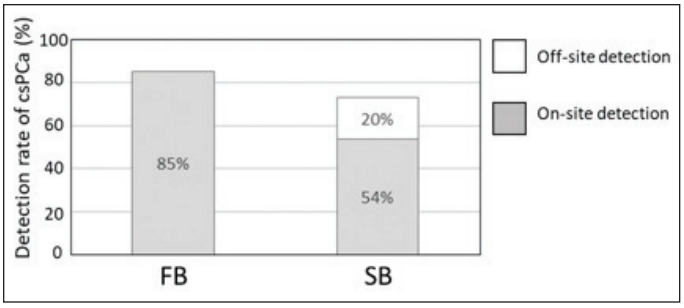

Fig. 2. Comparison of detection sites of clinically significant prostate cancer (csPCa) between systematic (SB) and fusion (FB) biopsy. FB detected 85% of csPCa from targeted cores, and SB detected 74% of csPCa from non-targeted grid-based cores. 54% of csPCa were detected by SB cores taken from the corresponding zones in which the magnetic resonance imaging (MRI) lesions were located, while 20% were detected by SB cores taken from zones away from the lesions and deemed normal by initial MRI.

from high-quality, randomized data has upheld MRI FB as a possible new upfront screening pathway in biopsy-naive patients, with improved detection of clinically significant disease by up to 30%,[12-14,18] and reduced over-detection of low-risk disease.[12,13,18,19] This has led to widespread clinical adoption of MRI FB but optimal protocol is yet to be determined in those with previous negative biopsies. Men with prior negative biopsies and ongoing suspicion for prostate cancer represent a group of patients with a unique need for enhanced disease detection. The current standard requires these patients to undergo serial PSAs, physical exams, and repeat 12-core biopsies, an imperfect approach with the ongoing problem of inaccurate diagnosis.[15] Each additional biopsy increases risk of infection and sepsis,[20] as well as cost inefficiency.[9] MRI FB, therefore, is a potential solution that addresses these concerns for this specific group of patients, although no clear evidence exists to support safe omission of standard SB.

Our data highlights that a combined MRI FB and SB is needed for maximal cancer detection in the setting of previous negative biopsies. While SB showed a lower detection rate of significant disease compared to FB (76% vs. 85%, respectively) and higher over-detection of low-risk disease (27% vs. 10%, respectively), omitting SB would have resulted in failure to diagnose six (15%) cases of significant prostate cancer. These figures are in line with those reported in the literature. Recent multicenter studies showed that FB alone missed 9–21% of significant disease, which was detected by SB.[8,21,22] In men with prior negative biopsies, the limited available data also supports a combined biopsy approach for optimal cancer detection; 21% of clinically significant cancers were missed by FB in this group of patients with PSA ≥4,[23] and 32% in another study for patients with PI-RADS ≥2 MRI lesions.[24]

A second important consideration is the high degree of discordant pathology with either biopsy modality alone. In this study, congruence on Gleason score was only seen in 34% of cases; 28% had upgrade in Gleason scores with FB and 38% with SB. Relying on either FB or SB alone would have resulted in substantial understaging (38% vs. 28%, respectively). The differences in final Gleason score imply change in management in most cases, as the patients are subsequently placed in different risk groups. Specifically, FB alone would have led to misclassification of three (7%) cases of significant disease as benign, two (5%) as low-risk cancer, and four (10%) high-risk cancers as intermediate-risk. This discordance has been observed across multiple studies, with a frequency of misclassification by FB ranging from 9–25%.[22,23,25] Therefore, a combined approach would further enhance the diagnostic confidence in terms of both presence and grade of significant disease.

Several parameters were found to be predictive of biopsy outcomes. Overall, an abnormal prostate exam and higher PI-RADS score were associated with detection of significant cancer, consistent with findings by other groups.[8,21] FB was not affected by prostate volume or lesion location, factors which predicted poor detection by SB. First, increasing prostate volume as measured on MRI was associated with decreased sensitivity for cancer (p=0.046). Intuitively, the chance of randomly sampling cancerous tissue would be reduced in a large prostate consisting of volumous non-cancerous tissue. Secondly, SB performance in this study

Table 3. Crosstabulation comparison of highest Gleason score detected by MRI fusion and standard systematic biopsy

		MRI fusion biopsy							
		Benign	3+3	3+4	4+3	4+4	4+5	5+4	Total
Systematic biopsy	Benign	7	1	1	2	0	1	0	12
	3+3	4	1	2	0	2	1	0	10
	3+4	1	2	5	0	1	0	0	9
	4+3	2	0	5	3	1	0	0	11
	4+4	0	0	1	4	1	3	0	9
	4+5	0	0	0	0	1	1	0	2
	5+4	0	0	0	0	0	0	0	0
	Total	14	4	14	9	6	6	0	53

Green shading designates patients who had concordance between fusion and systematic results. Blue shading designates patients who had a higher Gleason score on fusion compared with systematic biopsies. Pink shading designates patients who had a higher Gleason score on systematic compared with fusion biopsies. MRI: magnetic resonance imaging.

was poor if a lesion was found in the anterior prostate, only detecting cancer in 35% of such cases compared to 70% with FB. This finding is well-demonstrated in other studies, which found that SB missed 25–100% of anterior tumors diagnosed by FB.[7,26,27]

In the current study, we found that 20% of patients with significant cancer were diagnosed by systematic biopsy cores taken outside of the zones where the lesions were located on MRI, two (4.9%) of which originated from the contralateral prostate gland, suggesting that significant disease existed in areas deemed normal by MRI. This is supported by a recent study, which showed that 16% of patients with normal MRI had significant prostate cancer on SB.[8] The PICTURE study, which focused on patients needing repeat biopsies, determined that MRI had a negative predictive value of 91%, implying that an MRI-only approach would miss at least 9% of clinically significant disease.[28]

Despite these findings supporting the use of SB in addition to FB, there may be valid reasons for the alternative — using FB alone. In this study, along with multiple others, FB detected more clinically significant cancers, led to much fewer clinically insignificant cancer, and required fewer biopsy cores. The priority in men with prior negative biopsies and ongoing suspicion for cancer, however, should be focused on maximal cancer detection despite the mild increase in the diagnosis of indolent disease. The grounds for omitting SB must be based on minimal perceived benefit, and the findings of this study revealed two possible scenarios in which SB is less useful: when the MRI-detected lesion is located anteriorly and when the prostate volume exceeds 50 ml. In either case, SB led to little additional detection of significant cancer and re-classification of risk category; in men with only anterior MRI lesions, SB resulted in no new diagnosis and three (14%) re-classifications from intermediate- to high-risk, and in those with prostate volume >50 ml, SB led to no new diagnosis and one (5.9%) re-classification from intermediate- to high-risk. Indeed, among the cases in this cohort diagnosed with significant disease by SB and missed by FB, the lesions were all located posteriorly in smaller prostates ranging from 25–48 cc, suggesting that it may be reasonable to omit SB in patients with anterior lesions and larger prostate sizes.

Limitations

There are several limitations in this study. First, this was a retrospective, single-center design, which led to limited sample size; larger prospective studies are needed to validate our findings. Secondly, both FB and SB were performed by the same urologist, who was not blinded by the MRI findings. Third, final surgical pathology was not available, therefore, the true diagnostic accuracy cannot be assessed. Lastly, the study excluded those without suspicious MRI lesions and included only those with negative prior biopsies and ongoing clinical suspicion of cancer, which lacked an objective threshold, and proceeding with MRI was at the discretion of the two experienced urologists.

Conclusions

Fusion biopsies were modestly superior in diagnosis of clinically significant cancer and reduced detection of indolent disease. A combined approach with additional systematic biopsy is needed for maximal detection and risk classification of clinically significant cancer among men with prior negative biopsies and ongoing suspicion for prostate cancer. Anterior tumors and large prostates were significant predictors of poor systematic biopsy performance and an MRI-fusion biopsy alone approach in these settings could be considered.

Competing interests: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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