Outcomes of MRI fusion-guided versus systematic standard prostate biopsies

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Introduction: *The current utility of MRI-fusion targeted biopsy as either an adjunct to or replacement for systematic template biopsy for the detection of clinically significant prostate cancer is disputed. The purpose of this study is to assess the current effectiveness of MRI-targeted versus systematic template prostate biopsies at two institutions and to consider possible underlying factors that could impact variability between detection rates in our patient population compared to others.*

Materials and methods: *A retrospective review from our prospectively maintained prostate cancer databases was conducted. Patients with prostate MRI lesions (PI-RADSv2) receiving concurrent systematic 12-core and MRI-fusion targeted biopsies were reviewed. Clinically significant cancer was considered to be Grade Group ≥ 2.*

Results: *A total of 457 patients were included in the analysis; 255 patients received their biopsy at Institution A and 202 at Institution B. Overall cancer detection rate was 68%; the clinically significant cancer detection rate was 34%. Both MRI-targeted and systematic biopsies identified unique cases of clinically significant prostate cancer that the other modality missed. Out of 157 cases of clinically significant prostate cancer, MRI-targeted biopsy identified 29/157 cases (18%) missed by systematic biopsy, while systematic biopsy identified 37/157 cases (24%) missed by MRI-targeted biopsy (p = .39). Individual biopsy performance was similar when stratified by active surveillance or prior biopsy status, PI-RADSv2 score, and institution.*

Conclusions: *MRI-fusion targeted and systematic biopsy each identified unique cases of clinically significant prostate cancer. Both biopsy modalities should be utilized in order to provide the greatest sensitivity for the detection of clinically significant prostate cancer.*

Key Words: MRI fusion, biopsy, prostate cancer

Introduction

While MRI targets are being increasingly used for prostate biopsy, the unique contributions provided by MRI-fusion prostate biopsies (FB) versus traditional systematic twelve-core biopsies (SB) continues to be debated. Data exists to support a combined approach to prostate biopsy (SB and FB in tandem), as well as a FB-only approach.[1-4] Numerous variables at the tumor, patient and institutional levels may account for differences seen in studies attempting to describe the role of FB in the detection of prostate cancer. Here we identify the independent contributions of FB and SB in detecting clinically significant prostate cancer at two separate institutions.

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Materials and methods

After obtaining IRB approval (HHC-2019-0231), we retrospectively reviewed electronic records to identify patients 18-89 years old who underwent concurrent FB and SB between July 2016 and April 2018. All FBs were performed using the UroNav system. We collected demographic, clinical, and pathologic data, including biopsy results, MRI results (PI-RADSv2,[5] and prior biopsy status (active surveillance (AS), biopsy-naïve, prior negative biopsy (PNB), or prior radiation treatment). Whenever a patient had more than one region of interest (ROI) targeted by FB, his highest PI-RADS score and highest grade group (GG) were used in the analysis. Similarly, the highest GG and highest PI-RADS score were used to compare FB versus SB.

The two biopsy modalities were compared overall and through subgroup analyses. Subgroup analyses included comparisons of FB and SB when stratified by institution, prior biopsy status (except for subgroup defined by prior radiation therapy which was too small for meaningful analysis), and PI-RADSv2 score; subgroup analyses of prior biopsy status and PI-RADSv2 score were undertaken both overall and stratified by site. A positive biopsy result was considered to be clinically significant when GG was ≥ 2. Given that current NCCN Guidelines list AS as an option for some GG2 prostate cancers, analyses were also performed using GG ≥ 3 as a cut off point for clinical significance.

Statistical analyses

Findings from FBs and SBs for (a) all cancer, (b) clinically significant prostate cancer (GG ≥ 2), (c) GG ≥ 3 cancer, and (d) clinically insignificant (GG1) cancer were analyzed using McNemar tests of related proportions. For patients with multiple ROIs, a positive finding for any ROI was considered positive. A positive finding through either method was used as the 'gold standard' definition of a detected cancer. These findings were then used to calculate detection rates for each method. The differences between proportions were analyzed using the McNemar test.

Within-person analyses using McNemar tests were done for each of the subgroups. As the same data set was used repeatedly, a Bonferroni correction was applied maintaining overall significance level of .05. In addition, patients from the two institutions were compared using a between-subject chi-square test of proportion or exact test for categorical data and Wilcoxon Ranked Sum tests for continuous data. SPSSv26 was used for analyses.

Results

A total of 457 patients were included in this analysis. Significant differences were observed for prior biopsy status, age and distribution of Gleason Grade Group, Table 1. Both FB and SB identified unique cases of clinically significant prostate cancer missed by the alternate modality, Table 2. Neither modality performed significantly better than the other; overall, SB missed 18% (29/157) and FB missed 24% (37/157) of all clinically significant prostate cancer cases (p = 0.39), Figure 1. SB missed 17% (13/77) of clinically significant prostate cancer in patients on AS, 11% (4/37) of clinically significant prostate cancer in biopsy-naïve patients, and 28% (11/39) of clinically significant prostate cancer in patients with a PNB. FB missed 27% (21/77) of clinically significant prostate cancer in patients on AS, 24% (9/37) of clinically significant prostate cancer in biopsy-naïve patients, and 15% (6/39) clinically significant prostate cancer in patients with a PNB. Neither biopsy modality performed significantly better than the other when patients were stratified by AS/prior biopsy status, Figure 1. Neither biopsy modality was superior, Figure 2.

PI-RADS information was available for 446/457 patients. Thirty-two percent of patients (144/446) had a PI-RADS 3 lesion, 45% of patients (200/446) had a PI-RADS 4 lesion, and 23% (102/446) had a PI-RADS 5 lesion. SB and FB each detected unique cases of clinically significant prostate cancer cases missed by the other modality, regardless of PI-RADS status, Figure 3. Overall, SB missed 24% (4/17) of clinically significant prostate cancer cases in PI-RADS 3 lesions, 21% (16/78) of clinically significant prostate cancer cases in PI-RADS 4 lesions, and 15% (9/60) of clinically significant prostate cancer cases in PI-RADS 5 lesions. FB missed 24% (4/17) of clinically significant prostate cancer cases in PI-RADS 3 lesions, 26% (20/78) of clinically significant prostate cancer cases in PI-RADS 4 lesions, and 20% (12/60) of clinically significant prostate cancer cases in PI-RADS 5 lesions. Neither biopsy modality performed significantly better than the other when patients were stratified by PI-RADS lesion grade, Figure 3. Performance did not differ significantly when stratified by institution.

SB and FB each contributed unique cases of prostate cancer when analyzing only GG ≥ 3 cases, with neither modality performing superiorly to the other. Overall, SB missed 24% (16/68) of all GG ≥ 3 cases, and FB missed 28% (19/68) of all GG ≥ 3 cases (p = 0.74). SB missed 22% (6/27) of GG ≥ 3 cases in

TABLE 1. **Demographic and clinical characteristics**

	Institution A (n = 255)	**Institution B (n = 202)**	**p value**
Age (median, IQR)	65 (59.8, 69.1)	67 (62.0, 72.0)	< .001[1]
PSA (median, IQR)	5.8 (4.3, 8.5)	6.1 (4.7, 8.9)	.25[1]
Biopsy status (n,%)			< .001[2]
AS	157 (61.6)	63 (31.2)	
Naïve	33 (12.9)	35 (17.3)	
Prior neg biopsy	61 (23.9)	102 (50.5)	
Prior XRT	4 (1.6)	2 (1.0)	
Biopsy results (n,%)			
Negative biopsies (n,%)	80 (31.4)	68 (33.7)	.60[3]
Positive biopsies (n,%)	175 (68.6)	134 (66.3)	
Gleason Grade Group (n,%)			
GGG1 (n,%)	100 (57.1)	52 (38.8)	
GGG2 (n,%)	46 (26.3)	43 (32.1)	.002[3]
GGG3 (n,%)	17 (9.7)	16 (11.9)	
GGG4 (n,%)	8 (4.6)	8 (6.0)	
GGG5 (n,%)	4 (2.3)	15 (11.2)	

PSA = prostate-specific antigen; IQR = interquartile range; AS = active surveillance; XRT = radiation; GGG = Gleason Grade Group; [1]Wilcoxon Rank Sum; [2]Fisher-Freeman Halton exact test; [3]Chi-square

		Standard Systematic Biopsy Results					
		No cancer	Gleason 6 (GGG1)	Gleason 3+4 (GGG2)	Gleason 4+3 (GGG3)	Gleason >4+3 (GGG4,5)	Totals
MRI/Fusion Biopsy Results	No cancer	148	86	11	4	3	252
	Gleason 6 (GGG1)	12	54	16	2	1	85
	Gleason 3+4 (GGG2)	5	17	40	6	3	71
	Gleason 4+3 (GGG3)	2	3	6	10	0	21
	Gleason >4+3 (GGG4,5)	0	2	3	4	19	28
	Totals	167	162	76	26	26	457

Pathology results for 457 patients undergoing concurrent MRI-targeted and systematic biopsy are shown. Darker shading represents a greater clinical difference between Gleason Grade Group (GGG) pathology results. Boxes without shading represent biopsy concordance.

Table 2. Cancer detection concordance and discordance.

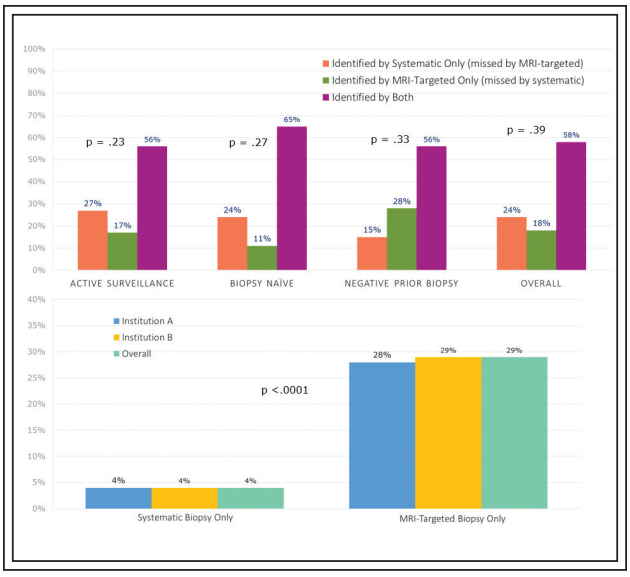

Figure 1. Systematic versus MRI-targeted biopsy. n = 457. Statistical comparisons made using McNemar test. **Top:** Percent of grade group ≥ 2 prostate cancer detected in all patients; **Bottom:** Percent of all patients with biopsy not positive for clinically significant prostate cancer, who would have clinically insignificant (grade group 1) diagnosis spared if they had received only one biopsy modality; p-value represents comparison between overall grade group 1 detection rates.

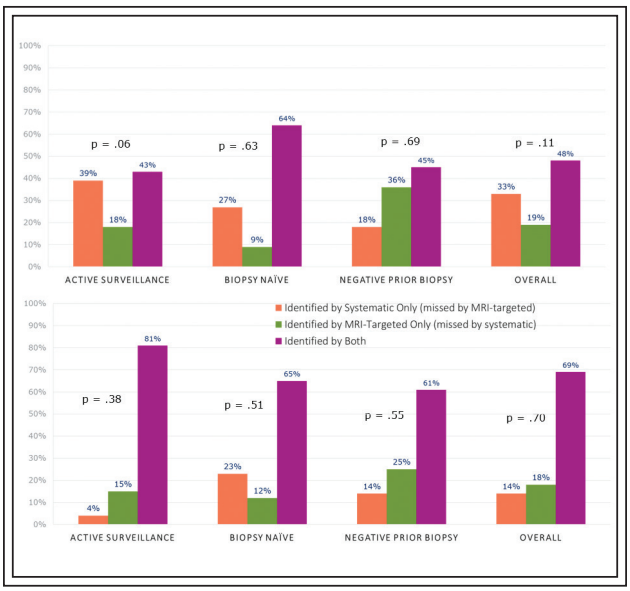

Figure 2. Detection of grade group ≥ 2 prostate cancer at individual institutions, stratified by prior biopsy and active surveillance status. Statistical comparisons made using McNemar test. **Top:** Institution A; **Bottom:** Institution B.

Figure 3. Prostate cancer detection rates by PI-RADSv2 score. **Top:** Results of all biopsy samples taken; **Middle:** Biopsy results positive for ≥ grade group 2 prostate cancer; **Bottom:** Percent of clinically significant (grade group ≥ 2) prostate cancer missed by systematic versus MRI-targeted biopsy by PI-RADSv2 score.

patients on AS, 18% (3/17) in biopsy-naïve patients, and 29% (6/21) in patients with a PNB. FB missed 41% (11/27) of GG≥3 cases in patients on AS, 24% (4/17) in biopsy-naïve patients, and 19% (4/21) in patients with a PNB.

With regard to GG1cancer, FB detected fewer cases compared to SB. Among patients in whom clinically significant prostate cancer was not found (n = 300), FB detected GG1 cancer in only 4% of patients (12/300) in whom SB found no cancer. Conversely, SB detected GG1 cancer in 29% of patients (86/300) in whom FB found no cancer (p < .0001). Eighteen percent of patients (54/300) had GG1 cancer identified on both SB and FB, and 49% (148/300) had no cancer detected by either modality. Unique detection of GG1 cancer by the two biopsy modalities was similar at each institution, Figure 1.

Discussion

In our study, both SB and FB identified a similar number of unique cases of clinically significant prostate cancer. This remained true for all patients regardless of prior biopsy status, PI-RADS score, institution, or the designation of clinically significant prostate cancer (≥ GG2 vs. ≥ GG3). Overall, SB uniquely identified 24% of clinically significant prostate cancer missed by FB, while FB uniquely identified 18% of clinically significant prostate cancer missed by SB ($p = 0.39$).

A number of single-center studies and one systematic meta-analysis have demonstrated that FB is associated with higher rates of detection of clinically significant prostate cancer and lower rates of detection of clinically insignificant cancers relative to SB.[6-9] In the multicenter, randomized PRECISION trial,[2] FBs identified 12% more cases of clinically significant prostate cancer, and spared an additional 13% of men a diagnosis of clinically insignificant prostate cancer, when compared to SB.[2] Similarly, the PROMIS trial found that FB was more sensitive than SB in the detection of clinically significant prostate cancer (93% vs. 48%, $p < .0001$), and concluded that in the absence of a suspicious lesion on MRI, SB may be omitted entirely.[1]

Other studies however suggest that FB should complement but not supplant SB. Two prospective studies found that FB and SB each identify unique cases of clinically significant prostate cancer that would be missed by utilizing either method alone.[3,4] One retrospective review of 506 patients that found that 16% of clinically significant prostate cancer (GG ≥ 2) would have been missed if SB were omitted.[10] A prospective trial of 2,103 patients found that out of 918 biopsies positive for ≥ GG2 prostate cancer, FB uniquely identified 268 cases (30%), while SB uniquely identified 123 cases (13%).[11] These figures are similar to our findings, in which 19% of clinically significant prostate cancer would have been missed if SBs were omitted.

The increased detection rate of GG1 cancers on SB should not be overlooked. One out of every five patients biopsied in our entire cohort received a diagnosis of GG1 prostate cancer based on SB alone. Ultimately, however, the goal of prostate biopsy is to detect clinically significant prostate cancer. We feel that the cases of clinically significant prostate cancer identified uniquely on SB outweigh the cases of GG1 cancer and warrant its continued use. Nonetheless, clinicians should consider this burden of "over-diagnosis" on patients, as well as increased healthcare costs, when counseling patients being evaluated for prostate biopsy.[12]

Particularly when considering the conclusions of the PROMIS[1] and PRECISION[2] trials, the role of including systematic biopsy cores as a component of a targeted biopsy program is subject to scrutiny. If institutions are able to prove acceptable detection rates of clinically significant prostate cancer with MRI-targeted cores alone, then systematic biopsy cores could reasonably be excluded, especially in light of the over-diagnosis of GG1 prostate cancer attributable to their inclusion. However, given the large number of patients at each institution analyzed in this study who would have had their clinically significant prostate cancer missed if systematic biopsy cores were excluded, the authors feel that combined MRI-targeted and systematic biopsies remains the preferred approach for this patient population.

The emergence of well-designed studies showing varying levels of cancer detection rates with FB and SB suggests that a variety of factors likely impact the accuracy and utility of either biopsy modality. For example, we noted considerable variability in prior biopsy status. At Institution A, 62% of patients received their biopsy on AS, whereas at Institution B, only 31% of patients were on AS ($p < .001$). The two largest positive trials advocating the superiority of FB over SB included only patients who were biopsy-naïve.[1,2] In our study, only 15% of patients (68/457) were biopsy-naïve. Nonetheless, FB performed no better amongst these patients when compared to patients on AS or patients with a PNB.

We noted other sources of variation that could impact cancer detection rates of FB and SB. At Institution A, multiple urologists perform FB, whereas at Institution B, all data came from a single urologist. Urologist proficiency is an inherent source of variability in any procedure and could impact cancer detection rates of FB. Additionally, an experienced urologic ultrasonographer performs SB at Institution A which could increase the site's ability to identify hypoechoic areas and impact cancer yield on SB.

Other sources of variability are related to personnel in radiology and pathology. In our study, a lack of radiology or pathology centralization can be viewed as either a limitation or an asset. Variability in reporting of prostate MRIs between radiologists has been associated with significant differences in both PI-RADS scores[13,14] and clinically significant prostate cancer detection rates on prostate biopsies.[13] Furthermore, many larger studies assessing FB have been conducted at large academic institutions where MRIs are read by either a single[15,16] or select few[17] designated uro-radiological experts. This situation is not indicative of the practice environment at many centers offering FB,

including ours. Inter-observer agreement on Gleason grading by pathologists is also subject to considerable variability.[18,19] As our study includes two institutions that obtained similar results with varying urologists, radiologists, and pathologists, we feel it may be more generalizable than many previously published studies using one or a select few expert readers.

Conclusions

FB and SB resulted in similar detection rates of clinically significant prostate cancer and neither outperformed the other at either institution. Although SB did detect more cases of GG1 prostate cancer (unique GG1 disease), this was outweighed by the number of clinically significant prostate cancer that would be missed if SBs were omitted. Our data supports concurrent FB and SB as the better paradigm for detecting clinically significant prostate cancer. □

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