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Comparative Effectiveness of Targeted Prostate Biopsy Using MRI-US Fusion Software and Visual Targeting: a Prospective Study

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Abstract

Purpose—To compare diagnostic outcomes between 2 different techniques for targeting regions-of-interest on prostate multiparametric Magnetic resonance imaging (mpMRI); MRI-ultrasound fusion (MR-F) and visually targeted (VT) biopsy.

Materials and Methods—Patients presenting for prostate biopsy with regions-of-interest on mpMRI underwent MRI-targeted biopsy. For each region-of-interest two VT cores were obtained, followed by 2 cores using an MR-F device. Our primary endpoint was the difference in the detection of high-grade (Gleason ≥ 7) and any-grade cancer between VT and MR-F, investigated using McNemar's method. Secondary endpoints were the difference in detection rate by biopsy location using a logistic regression model, and difference in median cancer length using Wilcoxon sign-rank test.

Results—We identified 396 regions-of-interest in 286 men. The difference in high-grade cancer detection between MR-F biopsy and VT biopsy was -1.4% (95% CI -6.4% to 3.6% ; $p=0.6$); for any-grade cancer the difference was 3.5% (95% CI -1.9% to 8.9% ; $p=0.2$). Median cancer length detected by MR-F and VT were 5.5mm vs. 5.8mm, respectively ($p=0.8$). MR-F biopsy detected 15% more cancers in the transition zone ($p=0.046$), and VT biopsy detected 11% more high-grade cancer at the prostate base ($p=0.005$). Only 52% of all high-grade cancers were detected by both techniques.

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Conclusions—We found no evidence of a significant difference in the detection of high-grade or any-grade cancer between VT and MR-F biopsy. However, the performance of each technique varied in specific biopsy locations, and the outcomes of both techniques were complementary. Combining VT biopsy and MR-F biopsy may optimize prostate cancer detection.

Keywords

Prostate cancer; MRI; Image-Guided Biopsy

Introduction

Prostate cancer (PCa) is a common, but clinically heterogeneous disease, with more than 900,000 cases diagnosed globally each year¹. The current diagnostic standard is systematic transrectal ultrasound (TRUS)-guided prostate biopsy, which is limited due to its random nature and risk of undersampling^{2,3}. The diagnostic accuracy of prostate Magnetic Resonance Imaging (MRI) has improved with the addition of functional sequences as part of multiparametric MRI (mpMRI). Increasing evidence now supports the role of mpMRI to identify high grade prostate tumors^{4, 5}.

Although recent studies have suggested that the use of MRI-targeted biopsy may improve cancer detection^{6–10}, the optimal technique to target the suspicious Regions-of-Interest (ROI) on mpMRI is still a matter of debate¹¹. MRI-targeted biopsy techniques (where mpMRI is used to determine the location of suspicious targets) can be classified in one of three categories: visual targeting (VT), where the operator biopsies a visually estimates an area on ultrasound that corresponds to the location of the ROI on MRI; MRI-Ultrasound fusion biopsy (MR-F) where pre-biopsy mpMRI images are superimposed with real-time ultrasonography during prostate biopsy using computer software; and direct in-bore, where the biopsy is performed inside the MRI scanner. Although MR-F takes advantage of existing experience of operators using TRUS and enables wide dissemination with physicians, the potential benefits of MR-F must be weighed against a steep learning curve, time investment, and costs^{12–14}. Two recent trials compared the diagnostic accuracy of MR-F biopsy to VT biopsy, and failed to detect a significant difference in the overall detection of clinically significant PCa^{15,16}. Other investigators have found that the use of VT can also improve sampling efficiency without the costs of the MR-F devices¹⁷.

Our objective was to compare diagnostic outcomes between MR-F and VT biopsy in terms of PCa detection rates, cancer detection by biopsy location within the prostate, and tumor length yield, in a prospective study.

Materials and Methods

Patient Cohort

After obtaining Institutional Review Board approval, consecutive men who presented for prostate biopsy underwent a prostate mpMRI at our institution. Patients were offered enrollment in this prospective study if one or more Regions-of-Interest (ROI) were identified

on mpMRI (MRI score ≥ 3). All included patients provided informed consent. In total, 296 men comprised the final cohort

MRI acquisition and analysis

MRI studies were performed at our institution, at least 3 months after the previous biopsy (in patients who had a previous biopsy), on a 3-T (n=262; 92%) or 1.5-T (n=24; 8%) MRI system (GE Healthcare, Wisconsin USA), using a multichannel phased-array coil. The following sequences were acquired: transverse T1-weighted images; transverse, coronal, and sagittal T2-weighted images; transverse diffusion-weighted sequences and parametric maps of apparent diffusion coefficients; 88% also had and a dynamic contrast-enhanced 3D T1-weighted spoiled gradient-echo sequence after IV injection of 0.1 mmol of gadopentetate dimeglumine (Magnevist, Berlex Laboratories) per kilogram of body weight. Acquisition parameters in msec (range) for T1-weighted images were TR (416 – 816.668), TE (6.176 – 14.532), slice thickness (3 – 5), interslice gap (0 – 2) and field of view (256×256 – 512×512); for T2-weighted images TR (2916.67 – 6766.67), TE (113.28 – 124.608), slice thickness (3 – 4), interslice gap (0) and field of view (256×256 – 512×512), and for DWI TR (3500 – 8200), TE (61.1–101.2), slice thickness (3–4), interslice gap (0) and field of view (256×256 – 512×512); b values used were 0 and 1000. mpMRIs were evaluated a per standard clinical care by one of 6 members of our institutions genitourinary radiology section, with 6 to 15 years of experience in prostate MRI. ROI suspicious for prostate cancer detected on mpMRI were graded per standard of care at our institution using a 5-item suspicion Likert scale as previously described^{18–20}. This scale was developed and validated in our institution using whole-mount prostatectomy specimen. The recently developed prostate imaging reporting and data system (PI-RADS) is an expert consensus statement and still undergoing wide validation. It is not used at our institution at present and therefore not evaluated in this study where standard of care mpMRI interpretation was assessed. All ROI considered suspicious by the interpreting radiologist (ie. subjective probability of cancer $\geq 50\%$ [MRI score ≥ 3]), were marked on the T2-weighted images for subsequent fusion with the ultrasound software.

Biopsy

MRI-targeted prostate biopsies were performed by two surgeons (BE, JC) from January 2014 through January 2015. Using a standardized protocol, each patient underwent VT biopsy under TRUS guidance. This was followed directly by MR-F biopsy, using a computer-assisted elastic image fusion system with real-time 3D tracking technology (UroStation; Koelis, Grenoble, France). The number of biopsy cores obtained for VT and MR-F was equivalent for each ROI (two cores under VT and two cores using MR-F; for a total of 4 biopsy cores obtained from each ROI). The investigator didn't have access to the VT biopsy during MR-F biopsy, as the target was identified on a separate monitor that doesn't project an ultrasound image; and biopsies were directed based only on software images. All pathology was reviewed by uro-pathologists specialized in prostate cancer.

Statistical analysis

To assess whether the MR-F biopsy results in a higher rate of cancer detection we investigated the difference in the rate of any-grade and high grade prostate cancer (Gleason

Grade 7) between the two biopsy techniques. We first assessed the difference in cancer detection on the patient level. For patients who had multiple ROI biopsied the highest grade ROI was utilized for the analysis. McNemar's method was used to compare the rates of cancer detection by biopsy method.

In a secondary analysis, we evaluated the difference in detection rate among all biopsied ROI. To account for the correlation among patients with multiple ROI, a mixed-effect logistic regression model was fit with a random intercepts within patient and within ROI. Clustered bootstrap methods were used to estimate the confidence interval about the difference in cancer detection. We included an interaction term in the model with type of biopsy (VT vs MR-F) and ROI location (Apex, Base, Mid, or Transitional Zone) to assess whether the detection rate was different by biopsy location.

We also assessed whether MR-F biopsy lead to increased millimeters of prostate (mm PCa) cancer being found compared to VT biopsy. For patients with multiple ROI biopsied, the mm PCa was calculated based on the highest grade core. Wilcoxon sign-rank test was used to test for the difference. All analyses were conducted in Stata 13.0 (StataCorp, College Station, TX).

Results

Patient cohort

Overall, the median age was 63 years (IQR 57–69), with a median pre-biopsy PSA of 5.3 (IQR 3.7–7.9, see Table 1). One hundred eighty-six (65%) men had a prior positive biopsy for PCa, 75 (26%) were biopsy naïve, and 16 (5.6%) had a prior negative biopsy. Nine of the men received prior treatment for prostate cancer. One-third of the men had more than one suspicious prostate ROI on MRI. Seventy-five percent of the ROI were graded as suspicious or consistent with tumor (i.e. MRI score 4/5 and 5/5, respectively).

Detection of high-grade or any-grade cancer

The VT biopsy identified 78 and the MR-F biopsy 74 patients with at least one high grade cancer among 286 patients (difference –1.4%; 95% confidence interval [CI] –6.4% to 3.6%; $p=0.6$). There were no significant differences in the detection of any grade cancer (difference 3.5%; 95% CI –1.9% 8.9%; $p=0.2$). When comparing all 396 biopsied ROI, we did not identify a statistically significant difference in high grade cancer detection (difference –2.0%; 95% CI –6.1% to 2.0%; $p=0.3$) or any grade cancer (difference 3.5%, 95% CI –1.6% to 8.3%, $p=0.11$). Although the overall detection rate of high grade cancer was not significantly different between the two modalities, the patients who were found to harbor cancer were not the same by both biopsy modalities. Of the 114 high grade tumors detected, the VT biopsy identified 90 (79%) high grade cancers and MR-F biopsy identified 82 (72%) high grade cancers, but only 59 (52%) of the tumors were found by both biopsies. (Table 2)

Tumor detection by biopsy location

We explored if the differences in the detection of high grade cancer by both modalities was associated with the location of the ROI targeted in the prostate gland. Despite not achieving

conventional definition of a statistically significant association, we did observe a trend suggesting a difference between the rate of prostate cancer detection and the location of the biopsied ROI ($p=0.083$). Moreover, in the subgroup analysis comparing performance of both techniques in each location, MR-F biopsies identified more cancer in the transitional zone compared to VT biopsies (Table 3 and Figure 1); however, the detection of any grade cancer did not differ significantly between VT and MR-F techniques in the apex, base, or mid zones. VT biopsies detected more high grade cancers at the base than MR-F biopsies ($p=0.005$), and no significant differences were detected for high grade cancer in the apex, mid, or transitional zones.

Tumor length assessment

We assessed if either targeting technique would confer an advantage in regards to tumor core length detected on biopsy. In regards to tumor volumes, among patients with positive VT or MR-F positive biopsy, VT biopsy detected a median 5.8mm of cancer compared to 5.5 mm by MR-F biopsy (difference 0.3; 95% CI -1.8 to 2.0 ; $p=0.8$).

Discussion

In this study comparing two techniques to perform MRI-targeted biopsy, we did not find a significant difference in the overall detection rate of any-grade or high grade prostate cancer using VT vs MR-F biopsy. However, while the overall detection rates were similar for both techniques, the tumors detected were not the same ones; only about half of the tumors were detected by both techniques. This finding is further supported by a trend suggesting a difference in detection rates by biopsy location, with MR-F detecting more tumors in the transition zone, and VT detecting more high-grade tumors in the prostate base. Our study provides incremental knowledge regarding the performance of MRI-targeted biopsy; while MR-F does not appear to detect more tumors than VT, it does seem to detect tumors that are difficult to visually target, such as those in the transition zone, which suggest that combining both techniques may improve prostate cancer detection. Nevertheless, this could potentially be explained by the increased number of cores obtained. The number of cores obtained for each strategy was arbitrarily decided in this study; the optimal number of cores remains to be determined.

Our results are in line with the primary findings of two recent prospective trials comparing the efficacy of MR-F vs. VT^{15,16}; there does not seem to be a clinically meaningful difference in the overall rate of prostate cancer detection using either technique. However, there are distinct differences to note in the design and patient cohort of each study. Puech et al¹⁵ compared the cancer detection rates MR-F to VT in 95 men without a prior prostate biopsy and found no significant difference between the two techniques. However, only 72% of the men underwent both a MR-F and VT, which limits the power in that study to detect a difference in detection rate between techniques. Wysock et al¹⁶ compared 125 men who underwent an MR-F by one urologist followed by a VT and standard 12 core biopsy by a second blinded urologist. The population was mixed and included men who were biopsy naïve, had a negative prior biopsy, and those on active surveillance. In that cohort, the authors found a trend toward improved prostate cancer detection and high grade PCa

sampling with MR-F compared to VT, although the differences were not significant. The study was well-constructed and blinded with two experienced urologists, although a large proportion had ROI on MRI that were of low suspicion for cancer; 67% had a PIRADS 3 grade or less with most ROI less than 1cm in diameter. As such, the Wysock et al cohort may have been limited by a cohort of men at low risk for prostate, specifically high risk tumors, to show a benefit from targeted MR-F techniques. In our study, we did find an improvement in the ability to sample a suspicious ROI in the transition zone with MR-F compared to VT. However, this improvement did not apply to the detection of high grade PCa, where VT had increased high grade cancer detection rates in the prostate base compared to MR-F. Wysock et al¹⁶ found that MR-F may improve targeting of ROI that are difficult to target on a standard biopsy, including anterior ROI. This may provide evidence for the utilization of MR-F in men who have difficult to target ROI on mpMRI, or in men with prior negative biopsies with persistently elevated PSA levels that may be harboring an anterior tumor. Moreover, more conspicuous ROI may have been better visible as hypoechoic area on ultrasound during VT biopsy, thus mitigating the benefit of software registration technology to direct MR-F biopsies. However, the improvement in high-grade detection prostate cancer with the VT technique at the base of the prostate may suggest either a limitation with registration software contouring to the base of the prostate or technical difficulty targeting the base of the prostate in axial orientation of the ultrasound probe. Specifically, the prostate undergoes varying degrees of compression and current elastic registration techniques may be limited to the extent of contouring at the base in which the prostate is significantly compressed with axial ultrasound-guided biopsies. Although the study by Wysock et al¹⁶ and the current study have different patient populations (large biopsy naïve population versus a large active surveillance cohort), these results show that there may be some differences in the respective abilities of MR-F and VT biopsies to detect prostate cancer in different locations in patients on active surveillance and biopsy naïve patients, and would warrant further investigation.

Several limitations of this study should be considered. Importantly, the MR-F and VT biopsy data were not compared to whole-mount prostatectomy specimens or appropriate follow-up, which may limit the clinical significance of negative biopsy findings. The software system used only enables a sphere to be overlayed on the ROI on MRI rather than contouring the target with the borders of the ROI. We are uncertain to what degree different software registration devices or biopsy techniques (transperineal) may impact our results. Finally, MR-F and VT were performed by high-volume urologists with extensive experience in MRI and both MR-F and VT, which may bias the results in favor of VT. We believe our study provides further insights regarding the specific patients that could benefit the most from these techniques. Our findings also suggest there is room for improvement of software registration and platforms, particularly for tumors located in the prostate base, where VT outperformed MR-F. Further research should investigate the accuracy of staging with either technique when compared to a gold-standard such as whole mount radical prostatectomy specimens

Conclusions

We found no evidence of a significant difference between VT and MR-F biopsy in the detection rate of high-grade or any-grade cancer. However, the performance of each technique varied in specific biopsy locations, and the outcomes of both techniques were complementary. Combining VT biopsy and MR-F biopsy may optimize prostate cancer detection.

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List of Abbreviations

MRI	Magnetic resonance imaging
mpMRI	Multiparametric magnetic resonance imaging
MR-F	Magnetic resonance - Ultrasound fusion
PCa	Prostate cancer
ROI	Region-of-interest
VT	Visually targeted

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Figure 1. Difference in Rate of Cancer Detection by Biopsy Location with 95% confidence interval. Positive differences indicate a higher rate of cancer detection using the MR-F biopsy.

Table 1

Patient Characteristics. Statistics presented are median (IQR) or frequency (percent).

N=286	
Age at Biopsy (years)	63 (57, 69)
Pre-biopsy PSA (ng/ml)	5.3 (3.7, 7.9)
Total Number of ROI for a Patient	
1	188 (66%)
2	87 (30%)
3	10 (3.5%)
4	1 (0.3%)
Biopsy Indication	
Confirmation Biopsy	186 (65%)
Elevated PSA	75 (26%)
Previous Negative Biopsy	16 (5.6%)
Post-Radiation Therapy	7 (2.4%)
Post-Cryoablation	2 (0.7%)
Highest mpMRI Score for a patient (N=285)	
3	71 (25%)
4	195 (68%)
5	19 (6.7%)

Table 2

Pattern of high grade and any grade cancer found (all ROI).

A) High grade cancer		
	MR-F Biopsy	
VT Biopsy	High Grade	No Cancer/Low Grade
High Grade	59	31
No Cancer/Low Grade	23	283

B) Any Grade Cancer		
	MR-F Biopsy	
VT Biopsy	Cancer	No Cancer
Cancer	100	31
No Cancer	45	220

Table 3

Rate of Any-Grade Cancer Detection by ROI Location. Bolded p-value tests for a difference in detection rate among the ROI locations.

ROI Location	MR-F Biopsy	VT Biopsy	Difference	95% Confidence Interval	p-value
<i>Any grade cancer</i>					
Apex (N=75)	29 (39%)	29 (39%)	0.0%	-13% – 13%	<i>0.083¹</i>
Base (N=71)	19 (27%)	23 (32%)	-5.6%	-16% – 4.2%	1
Mid (N=198)	69 (35%)	59 (30%)	5.1%	-1.6% – 12%	0.2
T-Zone (N=52)	28 (54%)	20 (38%)	15%	0.0% – 31%	0.090
<i>High grade cancer</i>					
Apex (N=75)	23 (31%)	19 (25%)	5.3%	-4.7% – 15%	<i>0.060¹</i>
Base (N=71)	9 (13%)	17 (24%)	-11%	-20% – -4%	0.3
Mid (N=198)	35 (18%)	38 (19%)	-1.5%	-7.3% – 4.1%	0.005 ²
T-Zone (N=52)	15 (29%)	16 (31%)	-1.9%	-14% – 8.8%	0.6
					0.7

¹ P-value testing for differences in cancer detection rate among ROI location.

² Calculated using bootstrap methods.