Am J Clin Exp Urol 2024;12(5):323-330
www.ajceu.us /ISSN:2330-1910/AJCEU0158708

Original Article

Prioritizing precision: detection of prostate cancer using mri guided fusion needle biopsy across the pennsylvania urologic regional collaborative

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Received June 24, 2024; Accepted October 15, 2024; Epub October 15, 2024; Published October 30, 2024

Abstract: Purpose: Targeted prostate biopsies are increasingly being performed by urologists in the United States including those in the Pennsylvania Urologic Regional Collaborative, a physician-led data-sharing and quality improvement collaborative. To evaluate the performance of MRI guided fusion needle prostate biopsies in the collaborative, we analyzed the variability by practice in rates of detection of clinically significant prostate cancer and patient characteristics associated with detection of clinically significant prostate cancer. Methods: We analyzed 857 first-time MRI fusion biopsy procedures performed at five practices (minimum 20 procedures) between 2015 and 2019. We used chi-square analysis for baseline patient characteristics and Grade Group (GG) ≥ 3 tumor detection rates by practice. Multivariable logistic regression was used to estimate the odds of clinically significant cancer detection when adjusting for baseline patient characteristics. Results: Approximately 15% of men undergoing targeted MRI guided biopsy were ≤ 59 years old. Median prostate specific antigen (PSA) was 6.8 ng/ml. Detection rates for GG ≥ 3 tumors ranged from 14.3% to 28.3% (P = 0.02) across practices. However, the odds of GG ≥ 3 tumor detection did not differ significantly between practices after adjusting for clinical and radiographic factors. Overall, increased likelihood of detecting a GG ≥ 3 tumor was associated with increased age, DRE abnormalities, higher PSA, smaller gland volume and PI-RADS ≥ 4 MRI lesions. There was an 81% concordance rate between PI-RADS ≥ 4 and Gleason grade ≥ 3 prostate cancer. Conclusion: We demonstrate the value of obtaining pre-biopsy MRI given high concordance between presence of suspicious lesions and MRI-targeted biopsy detection of clinically significant prostate cancer. Variability of baseline patient characteristics among practices may account for the observed differences in clinically significant cancer detection rates. These findings can aid standardization and quality improvement efforts within the collaborative.

Keywords: Prostate biopsy, fusion biopsy, prostate MRI, PI-RADS, PIRADS, TRUS biopsy, prostate cancer, detection, risk factors, clinically significant

Introduction

Targeted prostate biopsy using magnetic resonance imaging (MRI) fusion is increasingly being performed by urologists in the United States. In 2016, an estimated 60% of urologists in the United States reported performing magnetic resonance imaging/ultrasound (MRI/US) guided fusion prostate biopsies [1]. Emerging evidence suggests that MRI fusion biopsy is superior to conventional TRUS guided biopsy at detecting clinically significant prostate cancer with proportional decreased detection of low-risk cancers [2-5].

As opposed to systematic biopsy which samples tissue in all areas of the prostate, targeted MRI biopsy samples specific lesions that are suspicious for cancer based on multiparametric MRI imaging. The Prostate Imaging Reporting and Data System v2 (PI-RADS) grading system is used to grade lesions visualized on prostate MRI, in which associated risk of clinically significant prostate cancer for PI-RADS 1 is 2% (95% CI: 0%-8%), PI-RADS 2 is 4% (1-9%), PI-RADS 3 is 20% (13-27%), PI-RADS 4 is 52% (43-61%), and PI-RADS 5 is 89% (76-97%) [6].

Three methods of performing targeted biopsy using MRI fusion have been described: 1) cogni-

https://doi.org/10.62347/BPCP1813

tive fusion, where ultrasound guidance is used to aim the biopsy needle at the area where a lesion is demonstrated on review of the multiparametric MRI; 2) software-assisted MRI-ultrasound fusion, where the MRI image of the prostate is superimposed on real-time ultrasound image of the prostate while biopsy samples are collected; and 3) MRI-MRI fusion biopsy, otherwise called 'in-bore' biopsy, where diagnostic quality MRI images are fused with real-time interventional MRI images while biopsy is performed [7, 8]. All three methods produce comparable results, but cognitive-fusion and software-assisted fusion are more practical for most urologists as access to ultrasound and associated equipment is far more readily available than an interventional MRI imaging suite [8].

Magnetic resonance imaging guided fusion biopsy is a technically complex, multistep process, the accuracy of which depends on several factors including the quality of the multiparametric MRI, interpretation of the imaging, and the biopsy technique [9, 10]. The combination of these factors influences the result of any MRI fusion biopsy, so the results should be correlated with patient characteristics and traditional risk factors such as age, Black ancestry, digital rectal examination (DRE) findings, prostate specific antigen (PSA) level and prostate volume [10-12].

MRI-targeted fusion biopsy has a moderate recommendation (evidence level grade C) from the American Urologic Association (AUA) guidelines for biopsy-naïve patients and patients undergoing repeat biopsy with suspicious lesions (PI-RADS 3 to 5) [13]. For biopsy-naïve patients with a targetable PI-RADS 3 or greater lesion, combining targeted and systematic biopsy increases rates of Gleason-grade 1 prostate cancer detection and but yields little difference in Gleason-grade 2 or greater detection compared to a targeted-only approach [13]. For repeat biopsy with a targetable lesion, combined targeted and systematic biopsy cancer detection rates are 5-10% higher compared to targeted biopsy alone [13]. Therefore, the addition of systematic biopsy to targeted biopsy is optional in the presence of a targetable PI-RADS 3 or greater lesion given the small incremental increase in detection probability coupled with the morbidity of obtaining more biopsy samples [13].

Methods

Study objectives

To evaluate the performance of MRI guided fusion needle prostate biopsies across the collaborative, we analyzed: (1) the variability by practice in rates of detection of clinically significant prostate cancer using MRI guided needle prostate biopsy, (2) the concordance by practice between high-risk lesions on MRI and clinically significant prostate cancer, and (3) the patient characteristics and risk indicators as sociated with detection of with clinically significant prostate cancer on MRI guided fusion needle prostate biopsy.

Study population

The Pennsylvania Urologic Regional Collaborative (PURC) is a physician-led regional, data-sharing and quality improvement collaborative comprised of urology practices in Pennsylvania and New Jersey (https://hcifonline.org/program/purc). The mission of the collaboration is reduction of variation in care delivery and utilization of services for men with newly diagnosed prostate cancer. At the time of this study, the collaborative was comprised of 9 practices.

At each site, trained clinical abstractors collect patient and care data from electronic medical records and submit data to a central clinical registry maintained by a private data management contractor. The registry includes data on patient demographics, comorbidities, laboratory test results, pathology, imaging, treatment, outcome, complications, and mortality. Periodic quality audits are performed by the PURC coordinating center - the Health Care Improvement Foundation (HCIF) to ensure data accuracy.

Data de-identified for patient and practice-related information from January 2015 to June 2019 were obtained from the PURC registry for this analysis. This time interval was selected as it represented the initial learning curve of MRI guided fusion biopsies in all practices. Of all biopsies done in 2019, 24% were MRI fusion guided needle biopsies, compared to 11% in 2016 and 3% in 2015.

The inclusion criteria were any patient who received MRI-targeted fusion biopsy as a first-time biopsy from 2015 to 2019. Exclusions were made for patients who had biopsy per-

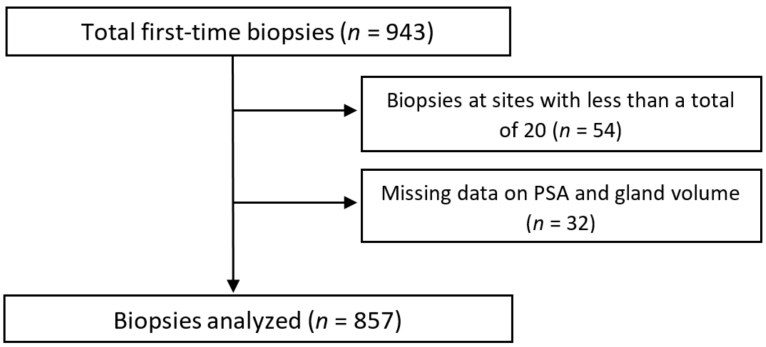

Figure 1. Flow diagram for participants included in study, Pennsylvania Urologic Regional Collaborative, 2005-2019.

formed at a site with less than 20 total MRI-targeted fusion biopsies during the study period and for patients missing data for any variables used in covariate analysis (age, race/ethnicity, family history of prostate cancer, digital rectal examination (DRE) findings, prostate specific antigen (PSA) level, prostate volume, and PI-RADS score). A total of 943 cognitive MRI or software assisted MRI-ultrasound fusion guided prostate biopsies were done for biopsy naïve patients during the study period. Data from 4 practices with less than 20 MRI guided fusion needle biopsy procedures performed during the study period were excluded from the analysis, leaving 889 biopsies. This procedure volume cutoff was chosen to ensure stability of the regression models and improve comparability of practices. Thirty-two patients with missing data for any covariates of interest were excluded from the analysis, leaving 857 biopsies in the final analytic sample (**Figure 1**).

Outcome assessment

The outcome of interest was MRI-guided fusion needle prostate biopsy showing clinically significant prostate cancer, defined here as a tumor of Grade Group (GG) ≥ 3 (Gleason score of ≥ 4+3). This definition meets the National Comprehensive Cancer Network (NCCN) criteria for unfavorable intermediate risk disease [14, 15].

Covariate assessment

Practice identifier (sites labeled as A through E) and patient-level risk indicators were included as covariates in the analysis. Risk indicators available from the PURC database included age (modeled as age groups ≤ 59 years, 60 to 69 years and ≥ 70 years), race/ethnicity, family history of prostate cancer, digital rectal examination (DRE) findings, prostate specific antigen (PSA) level, prostate volume, and pre-biopsy multiparametric MRI tumor risk assessment expressed as a PI-RADS score.

Statistical analysis

Chi-square tests examined the distribution of patient characteristics/risk indicators by practice, and the concordance between pre-biopsy multiparametric MRI high-risk tumor assessment (defined as PI-RADS ≥ 4 score) and GG ≥ 3 tumor by practice. Using a multivariable logistic regression model, we analyzed the association between practice, patient-level risk indicators and clinically significant cancer detection at targeted biopsy. Statistical analysis was done using SAS software version 9.4 (SAS Institute, Inc.; Cary, NC). Two-sided tests of hypothesis were performed throughout with alpha level of significance set ab initio to 0.05.

Results

Overall, 14.4% of patients who had targeted MRI guided biopsies were aged 59 years or younger, 77.7% were Non-Hispanic White, 28.4% had family history of prostate cancer, 12.7% had abnormal DRE findings on examination, and 34.7% had prostate volume greater than 60 cc. The median PSA was 6.8 ng/ml and 13.9% of patients had PSA less than 4 ng/ml. The distribution of age, race, family history, DRE finding, PSA and prostate volume of patients varied significantly by practice (**Table 1**). The proportion of patients with pre-biopsy MRI assessment of high-risk disease (PI-RADS ≥ 4) was 63.2%, ranging from 47.6% to 75.6% across practices (*P* value < 0.0001) (**Table 1**).

Grade Group 3 or higher tumors were detected in 23.2% of all patients, but the rate varied significantly across practices, ranging from 14.3% to 28.3% (*P* value = 0.02) (**Table 2**). Of all GG ≥ 3 or higher tumors diagnosed, 80.9% had a pre-biopsy MRI PI-RADS score of 4 or higher. The concordance rate between GG ≥ 3 tumors and PI-RADS ≥ 4 assessment also varied significantly across practices, ranging from 50% to 89.7% (*P* value = 0.003) (**Table 2**).

Table 1. Baseline characteristics of patients undergoing MRI guided fusion prostate biopsy, Pennsylvania Urologic Regional Collaborative, 2015-2019

	Overall N = 857	Practice A N = 42	Practice B N = 250	Practice C N = 233	Practice D N = 119	Practice E N = 213	*P* value
Age group (years)							
59 or younger	123 (14.4)	8 (19.1)	44 (17.6)	26 (11.2)	19 (16)	26 (12.2)	0.01
60-69	389 (45.4)	16 (38.1)	126 (50.4)	100 (42.9)	61 (51.3)	86 (40.4)	
70 or older	345 (40.3)	18 (42.9)	80 (32)	107 (45.9)	40 (32.8)	101 (47.4)	
Race							
Non-Hispanic White	666 (77.7)	33 (78.6)	213 (85.2)	169 (72.5)	101 (84.9)	150 (70.4)	< 0.0001
Non-Hispanic Black	114 (13.3)	9 (21.4)	25 (10)	44 (18.9)	4 (3.4)	32 (15)	
Other*	77 (9)	-	12 (4.8)	20 (8.6)	14 (11.8)	31 (14.6)	
Family History							
No	565 (65.9)	22 (52.4)	150 (60)	166 (71.2)	82 (68.9)	145 (68.1)	0.04
Yes	243 (28.4)	18 (42.9)	83 (33.2)	59 (25.3)	32 (26.9)	51 (23.9)	
Unknown	49 (5.7)	2 (4.8)	17 (6.8)	8 (3.4)	5 (4.2)	17 (8)	
DRE							
Normal	573 (66.9)	35 (83.3)	115 (46)	175 (75.1)	86 (72.3)	162 (76.1)	< 0.0001
Abnormal	109 (12.7)	7 (16.7)	14 (5.6)	39 (16.7)	30 (25.2)	19 (8.9)	
Unknown	175 (20.4)	-	121 (48.4)	19 (8.2)	3 (2.5)	32 (15)	
PSA (ng/ml)							
Median	6.8	8.0	6.1	6.6	7.8	7.6	
Less than 4	119 (13.9)	3 (7.1)	43 (17.2)	34 (14.6)	15 (12.6)	24 (11.3)	0.01
4-10	532 (62.1)	23 (54.8)	166 (66.4)	141 (60.5)	66 (55.5)	136 (63.9)	
Greater than 10	206 (24)	16 (38.1)	41 (16.4)	58 (24.9)	38 (31.9)	53 (24.9)	
Prostate volume (cc)							
Median	49	60	39.4	51	52	55.2	
Less than 30	125 (14.6)	2 (4.8)	58 (23.2)	30 (12.9)	13 (10.9)	22 (10.3)	< 0.0001
30-60	435 (50.8)	21 (50)	138 (55.2)	115 (49.4)	63 (52.9)	98 (46)	
Greater than 60	297 (34.7)	19 (45.2)	54 (21.6)	88 (37.8)	43 (36.1)	93 (43.7)	
PI-RADS ≥ 4							
Yes	542 (63.2)	20 (47.6)	165 (66)	163 (70)	90 (75.6)	104 (48.8)	< 0.0001
No	315 (36.8)	22 (52.4)	85 (34)	70 (30)	29 (24.4)	109 (51.2)	

* includes Hispanic/Asian/Native American/Unknown.

Table 2. Clinically significant prostate cancer detection rates and concordance with pre-biopsy MRI, Pennsylvania Urologic Regional Collaborative, 2015-2019

	Total N %	Practice A n %	Practice B n %	Practice C n %	Practice D n %	Practice E n %	*P*-value[a]
GG ≥ 3							
Yes	199 (23.2)	6 (14.3)	64 (25.6)	66 (28.3)	29 (24.4)	34 (16)	0.02
No	658 (76.8)	36 (85.7)	186 (74.4)	167 (71.7)	90 (75.6)	179 (84)	
PI-RADS ≥ 4				GG ≥ 3			
Yes	161 (80.9)	3 (50)	52 (81.3)	59 (89.4)	26 (89.7)	21 (61.8)	0.003
No	38 (29.1)	3 (50)	12 (18.7)	7 (10.6)	3 (10.3)	13 (38.2)	

[a]Chi-square *p*-value.

Multivariable analysis (**Table 3**) highlighted that after adjusting for pre-biopsy MRI, age, family history, race, DRE finding, PSA and prostate volume, the odds of detecting a GG ≥ 3 tumor on MRI guided prostate biopsy did not differ significantly by practice (*P* value = 0.11). Pre-biopsy

Table 3. Association between practice and patient-level risk indicators with clinically significant prostate cancer at MRI guided fusion needle prostate biopsy, Pennsylvania Urologic Regional Collaborative, 2015-2019

Risk factor	Crude OR (95% CI)		*P* value	Adjusted OR (95% CI)		*P* value
Practice			0.02			0.11
A	1	Referent		1	Referent	
B	2.07	0.83, 5.13		2.24	0.81, 6.18	
C	2.37	0.95, 5.89		2.13	0.80, 5.71	
D	1.93	0.74, 5.05		1.54	0.54, 4.39	
E	1.14	0.45, 2.91		1.25	0.45, 3.45	
PI-RADS ≥ 4			< 0.0001			< 0.0001
No	1			1	Referent	
Yes	3.08	2.09, 4.53		2.61	1.71, 3.98	
Age group (years)			< 0.0001			< 0.0001
59 or younger	1			1	Referent	
60-69	1.92	1.04, 3.54		2.11	1.08, 4.11	
70 or older	3.55	1.95, 6.47		3.91	2.03, 7.82	
Family History			0.32			0.47
No	1			1		
Yes	0.98	0.69, 1.39		1.19	0.79, 1.79	
Unknown	0.53	0.23, 1.21		0.70	0.29, 1.69	
Race			0.19			0.43
White	1	Referent		1		
Black	1.48	0.95, 2.29		1.37	0.82, 2.30	
Other[a]	0.91	0.51, 1.63		0.89	0.46, 1.75	
DRE			< 0.001			< 0.001
Normal	1	Referent		1		
Abnormal	2.42	1.56, 3.74		2.70	1.62, 4.49	
Unknown	1.11	0.73, 1.67		0.90	0.54, 1.50	
PSA (ng/ml)			< 0.0001			< 0.0001
Less than 4	1			1		
4-10	1.89	1.04, 3.43		2.46	1.30, 4.67	
Greater than 10	4.57	2.45, 8.54		7.34	3.65, 14.75	
Prostate volume (cc)			< 0.0001			
Greater than 60	1			1		< 0.0001
30-60	2.34	1.56, 3.49		3.09	1.97, 4.86	
Less than 30	4.54	2.77, 7.45		7.59	4.25, 13.58	

a includes Hispanic/Asian/Native American/Unknown.

PI-RADS score ≥ 4 was associated with increased odds of detecting a GG ≥ 3 tumor (OR 2.61; 95% CI 1.71-3.98). The odds of GG ≥ 3 tumor in men 70 years or older was 3.91 times that of men aged 59 years or younger (95% CI 2.03-7.82). Similarly, DRE finding, PSA and prostate volume were significantly associated with GG ≥ 3 tumor detection (**Table 3**).

Discussion

There remains concern about over and under diagnosis of prostate cancer. Graif et al., in their study of different cohorts of men undergoing radical prostatectomy between 1989 and 2005, estimated the overdiagnosis rate to be between 1.3% to 7.1% while the proportion of prostate cancer under diagnosed was between 25% and 30% [16]. Studies have shown that TRUS guided biopsy is associated with grade underestimation rates between 30% and 47.8% and grade overestimation rates between 9% and 18% [17-19]. Conversely, targeted MRI-guided fusion biopsy is associated with higher detection of clinically significant prostate can-

cer and lower detection of clinically indolent disease compared to TRUS guided systematic biopsy [20, 21]. This translates to lower under diagnosis rates with targeted MRI-guided fusion biopsies although underdiagnosis is still possible with poor targeting of a lesion. In one study, MRI-US fusion biopsy detected 30% more high-risk prostate cancer than TRUS biopsy and 17% fewer low-risk cancer [3]. In another study involving men with prior negative biopsies, TRUS-guided systematic biopsy missed 55% of Gleason ≥ 8 tumors which were detected on MRI-US fusion biopsy [5]. These findings may be explained by the technical nuances of both approaches.

In contrast to the targeted MRI guided fusion biopsy procedure, during TRUS-guided biopsy, multiple tissue samples are obtained in a random, systematic fashion from different regions of the prostate gland. The blinded and random nature of this process leaves room for sampling errors [22]. Given benefits of targeted MRI guided fusion needle prostate biopsies and its increasing uptake among urologists, assessing results across PURC practices is imperative to identifying areas of potential improvement and formulation of strategies to ensure effective and efficient deployment of the procedure.

In our study, the observed detection rates for Grade Group ≥ 3 tumors among biopsy naïve men differed significantly across PURC practices. At least part of this may be explained by results of the multivariable analysis, which demonstrated this variation was insignificant after adjusting for baseline patient characteristics like pre-biopsy MRI assessment, age, DRE finding, PSA and prostate volume. Importantly, the distribution of commonly studied prostate cancer risk indicators varied significantly across practices and were each independently associated with GG ≥ 3 cancer detection [23-26]. Taken together, this suggests possible inconsistency across practices when determining the patients to whom MRI-guided fusion needle prostate biopsy is recommended. For instance, while only 11.2% of patients undergoing MRI-guided fusion needle prostate biopsy at Practice 'C' were 59 years old or younger, the same proportion was 19.1% at Practice 'A' (**Table 2**). Simultaneously, GG ≥ 3 cancer detection rate was higher for Practice 'C' compared to Practice 'A' (**Table 1**). Similar parallels can be drawn for other risk indicators like DRE findings and pre-biopsy PI-RADS score.

Our study found that pre-biopsy multiparametric MRI assessment of PI-RADS 4 or higher was associated with increased likelihood of detecting clinically significant prostate cancer on MRI-guided fusion needle prostate biopsy (OR 2.61, 95% CI: 1.7, 3.98). This confirms the usefulness of multiparametric MRI risk assessment in the prostate cancer diagnostic process. As a standalone process, multiparametric MRI has been shown to have high sensitivity and negative predictive value for clinically significant prostate cancer [20, 21], indicating that it may be reliably employed in cancer risk assessment prior to recommending the more invasive prostate biopsy. The concordance rate between GG ≥ 3 tumors and pre-biopsy PI-RADS score also differed significantly by practice. This may also explain some of the variability in clinically significant cancer detection rates observed across practices as there appears to be some correlation between higher concordance rates and clinically significant cancer detection rates (**Table 2**).

The non-uniform distribution by practice of baseline patient characteristics may be an indication of differences in practice patterns regarding the selection of patients for MRI guided fusion needle prostate biopsies [12]. This finding is relevant to the mission of PURC to promote healthcare quality improvement and reduce variation in care delivery and service utilization in the region.

A strength of our study is that the data used was sourced from both academic and community-based urology practices, which allows for more generalizable results with regards to existing regional practice patterns. Furthermore, periodic data quality audits done by the PURC coordinating center, ensures that the research data is source-verified and of reliable quality.

Our study is not without limitations, however. First, our analysis did not separate targeted MRI guided prostate biopsies by specific technique: cognitive fusion, software-assisted MRI/US fusion, and "in-bore" MRI-guided biopsy. However, as earlier mentioned, research has yet to demonstrate any significant differences in biopsy results across these different biopsy techniques. Second, our analysis did not differentiate combined targeted and systematic biopsies from strictly targeted prostate biopsies because the data collected in the PURC

registry at the time of our study did not allow for such granularity. Systematic 12-core needle biopsy is often combined with targeted MRI fusion needle biopsy in the same procedure [27]. Third, our analysis did not control for practice-level factors such as practice size, practice setting (academic versus community-based), number of providers and level of provider experience. As the results of the multivariable analysis show, the variability in clinically significant cancer detection rates by practice was mostly accounted for by baseline characteristics of patients-level risk indicators.

Future directions of research should include further study of MRI-targeted biopsy technique comparison, specifically comparing differences in detection rates of cognitive MRI/US fusion and software-assisted MRI/US fusion. Larger studies are also needed to evaluate the risks and benefits of combined targeted and systematic biopsy compared to targeted biopsy alone in patients with a targetable lesion. Researchers should continue to use multivariate analysis in their study of these techniques as we demonstrated that baseline patient and clinical disease characteristics can significantly skew interpretation of data between study sites.

Conclusion

Our study found that rates of detection of clinically significant prostate cancers on MRI-guided fusion biopsy differed significantly by practice in PURC. The observed variability was mostly accounted for by differences in baseline characteristics of patients undergoing MRI guided fusion needle biopsies, suggesting that more uniform selection of patients for targeted biopsy across to collaborate would result in comparable cancer detection rates. These findings can aid standardization and quality improvement efforts within PURC, while providing information that could be useful to similar quality improvement projects elsewhere. Our study further supports the usefulness of pre-biopsy MRI in predicting clinically significant prostate cancer with an 81% concordance between PI-RADS $\geq$ 4 and Gleason grade $\geq$ 3.

Disclosure of conflict of interest

None.

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