Oncology

Intra-practice Urologist-level Variation in Targeted Fusion Biopsy Outcomes

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OBJECTIVE To examine the extent to which the urologist performing biopsy contributes to variation in prostate cancer detection during fusion-guided prostate biopsy.

METHODS All men in the Michigan Urological Surgery Improvement Collaborative (MUSIC) clinical registry who underwent fusion biopsy at Michigan Medicine from August 2017 to March 2019 were included. The primary outcomes were clinically significant cancer detection rate (defined as Gleason Grade ≥2) in targeted cores and clinically significant cancer detection on targeted cores stratified by PI-RADS score. Bivariate and multivariable logistic regression analyses were performed.

RESULTS A total of 1133 fusion biopsies performed by 5 providers were included. When adjusting for patient age, PSA, race, family history, prostate volume, clinical stage, and PI-RADS score, there was no significant difference in targeted clinically significant cancer detection rates across providers (range = 38.5%-46.9%, adjusted *P*-value = .575). Clinically significant cancer detection rates ranged from 11.1% to 16.7% in PI-RADS 3 (unadjusted *P* = .838), from 24.6% to 43.4% in PI-RADS 4 (adjusted *P* = .003), and from 69.4% to 78.8% in PI-RADS 5 (adjusted *P* = .766) lesions.

CONCLUSION There was a statistically significant difference in clinically significant prostate cancer detection in PI-RADS 4 lesions across providers. These findings suggest that even among experienced providers, variation at the urologist level may contribute to differences in clinically significant cancer detection rates within PI-RADS 4 lesions. However, the relative impact of biopsy technique, radiologist interpretation, and MR acquisition protocol requires further study. UROLOGY xx: xxx–xxx, xxxx. Published by Elsevier Inc.

There is Level 1 evidence supporting the use of multiparametric magnetic resonance imaging (MRI) and transrectal ultrasound-guided prostate biopsy (fusion biopsy) in the prostate cancer diagnostic pathway.[1-4] These studies have consistently demonstrated that the addition of targeted samples improves the detection of clinically significant (CS) prostate cancer over systematic biopsy alone. Consequently, European and the United Kingdom's National Institute for Health and Care Excellence guidelines have updated their recommendations to include the use of prostate MRI in the biopsy naive patient.[5] As such, there has been widespread, rapid adoption in the use of fusion biopsy.

While it is evident that fusion biopsy outperforms standard biopsy in cancer detection, rates with fusion biopsy range from 46% to 70%.[2,4] Prior work has demonstrated the impact of patient and imaging factors on cancer detection rate such as PSA, Prostate Imaging and Reporting Data System (PI-RADS) risk assessment category, family history, age, race, digital rectal examination (DRE), MRI image quality, image interpretation, and technical specifications of MRI acquisition.[6-8] However, it is not known the degree to which differences in biopsy technique contribute to variation in cancer detection.

As fusion biopsy becomes ubiquitous, it is beneficial to determine whether there is an ideal approach to optimize cancer detection.For instance, subtle differences across providers in sampling methods and techniques may introduce significant variation in cancer detection at the provider level.[9] Prior work in this area has identified variation in radiologist interpretation of MRI imaging; however, the literature has yet to address variation across biopsy providers.[7]

In this study, we used data from a cohort of experienced urologists at a single institution to investigate provider-level variation in fusion biopsy cancer detection

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rate. Although there are identifiable differences in technique and workflow, once fusion biopsy providers are experienced, subtle differences in biopsy technique may not result in variation across providers working with the same MRI units, acquisition parameters, and interpreting radiologists. For this reason, we hypothesize that there is no variation in fusion biopsy cancer detection rates across providers at a single center after controlling for patient-specific factors.

MATERIALS AND METHODS

All men in the Michigan Urological Surgery Improvement Collaborative (MUSIC) clinical registry who underwent fusion biopsy at Michigan Medicine from August 2017 to March 2019 for elevated PSA, abnormal prostate exam, or abnormal prostate MRI were included. Men with prior prostate cancer treatment, other than active surveillance, were excluded. The MUSIC clinical registry is maintained by trained data abstractors who enter a set of data elements for all men in MUSIC practices who undergo a prostate biopsy. Provider-level outcomes were analyzed. This study adheres to the Standards of Reporting for MRI-targeted Biopsy Studies (START) working group recommendations for reporting.[10]

Prostate MRI

Multiparametric MRI examinations performed within MUSIC were used for fusion biopsy targeting. All MRIs were performed according to PI-RADS v2 guidelines.[11] MRI examinations were performed on a 3-Tesla magnet using a 32-channel pelvic phased array coil (Philips Ingenia [Best, Netherlands] or Siemens Skyra [Munich, Germany]) without an endorectal coil. At a minimum, the following pulse sequences were acquired: axial/coronal/sagittal narrow field-of-view 2D T2-weighted fast spin echo centered on the prostate, axial diffusion-weighted imaging with a maximum b-value of at least 1500 s/mm^2 with automated apparent diffusion coefficient (ADC) map generation, axial T1-weighted dynamic contrast-enhanced imaging with a temporal resolution of 7 seconds or less, and wide field-of-view whole pelvis T1- or T2-weighted imaging. MR spectroscopy was not performed at any site.

All MRI examinations were interpreted according to PI-RADS v2 guidelines[11] using a structured report template. Reporting was performed by one of 13 radiologists with a range of experience from 1 to 22 years, as a part of routine clinical care. Prostate gland and lesion segmentation were performed at the time of interpretation using DynaCAD (Invivo/Philips Medical, Gainesville, FL).

Fusion Biopsy

Transrectal fusion biopsy was performed using an electromagnetically tracked biopsy platform (Uronav, Invivo/Philips Medical, Gainesville, FL). Elastic or rigid registration was used at the biopsy provider's discretion. Targeted cores, typically 2-4 cores per target, were obtained first, followed by standard systematic 12-core extended sextant biopsy by the same provider in the same session. Biopsy was performed by providers well outside the learning curve for fusion biopsy with each having performed > 50 fusion biopsies independently prior to the study period.[12]

Analysis

The primary outcome of interest was successful sampling of targeted lesions, defined as CS cancer detection by targeted cores. Additional outcomes of interest included CS cancer detection rate in targeted cores of PI-RADS 3, 4, and 5 lesions stratified by PI-RADS category and meeting MUSIC benchmark measures for cancer detection by fusion biopsy. CS prostate cancer was defined as Gleason Grade Group ≥2. MUSIC benchmarks were determined by expert consensus based on the available literature including published PI-RADS v2 validation studies from expert centers. MUSIC quality benchmarks for CS cancer detection rates are 10%-25%, 25%-60%, and 70%-95% for PI-RADS 3, 4, and 5 lesions, respectively.[13,14]

Our primary and secondary outcomes were analyzed by using bivariate and multivariable logistic regression analyses to assess variation in cancer detection rates at the fusion biopsy provider level controlling for patient age, PSA, race, family history, prostate volume, clinical stage, and PI-RADS score. *P*-values less than .05 were considered statistically significant. Each MUSIC practice obtained an exemption or approval for collaborative participation from a local institutional review board. Statistical analysis was performed using SAS 9.4.

RESULTS

We identified 1133 patients in the MUSIC registry who underwent fusion biopsy at the University of Michigan. These were completed by 5 providers who each performed between 161 and 306 fusion biopsies during the study period. There was no significant difference in distribution of age, race, family history, or PSA across patients treated by the 5 providers (Table 1). However, there were statistically significant differences in DRE, maximum PI-RADS score, prior diagnosis of prostate cancer, and number of cores obtained per lesion (Table 1). Prior to the study period, Providers A, B, C, D, and E had 220, 167, 115, 0, and 57 biopsies recorded in the MUSIC registry, respectively. Provider D was a new provider in MUSIC during the study period, so biopsies they performed prior to becoming a MUSIC provider were not captured in the registry. However, they had performed at least 50 fusion biopsies outside of the MUSIC registry prior to the study period.

There was no difference in CS cancer detection rates in targeted cores across biopsy providers (Table 2). Adjusted overall detection of CS prostate cancer with targeted cores on fusion biopsy ranged from 38.5% to 46.9% across the 5 providers (range = 8.5%, adjusted *P*-value = .575) with an average CS cancer detection rate of 43.0% (Fig. 1). CS cancer detection rates for all providers surpassed the MUSIC quality benchmark of > 35% for all PI-RADS categories combined.

Of the targeted lesions biopsied in this study, 307 were PI-RADS 3, 691 were PI-RADS 4, and 358 were PI-RADS 5. Detection of CS prostate cancer in PI-RADS 3 lesions ranged from 11.1% to 16.7% across the 5 providers (unadjusted *P* = .838) with an average CS cancer detection rate of 14.0%. Detection of CS prostate cancer in PI-RADS 4 lesions ranged from 26.6% to 43.4% across the 5 providers (adjusted *P* = .003) with an average CS cancer detection rate of 36.6%. Detection of CS prostate cancer in PI-RADS 5 lesions ranged from 63.5% to 78.7% across the 5 providers (adjusted *P* = .766) with an average CS cancer detection rate of 70.1% (Table 3). MUSIC quality benchmarks for CS cancer detection rates are 10%-25%, 25%-60%, and 70%-95% for PI-RADS 3, 4, and 5 lesions, respectively. CS cancer detection rates for all providers were within the MUSIC quality benchmarks for PI-RADS 3

Table 1. Patient-specific characteristics by fusion biopsy provider.

	Biopsy Provider A	B	C	D	E	*P*-value
No. patients	306	161	292	184	190	
Race						
White	277 (90.5%)	140 (87.0%)	249 (85.3%)	158 (85.9%)	166 (87.4%)	.427
Non-white	22 (7.2%)	18 (11.2%)	30 (10.3%)	22 (12.0%)	17 (8.9%)	
Unknown	7 (2.3%)	3 (1.9%)	13 (4.5%)	4 (2.2%)	7 (3.7%)	
Family history of PCa						
Yes	83 (27.1%)	49 (30.4%)	80 (27.4%)	43 (23.4%)	61 (32.1%)	.381
No/Unknown	223 (72.9%)	112 (69.6%)	212 (72.6%)	141 (76.6%)	129 (67.9%)	
DRE						
Positive	10 (3.3%)	11 (6.8%)	11 (3.8%)	19 (10.3%)	30 (15.8%)	< .001
Negative	235 (76.8%)	144 (89.4%)	263 (90.1%)	107 (58.2%)	150 (78.9%)	
Unknown	61 (19.9%)	6 (3.7%)	18 (6.2%)	58 (31.5%)	10 (5.3%)	
Prior diagnosis of PCa						
Yes	87 (28.4%)	33 (20.5%)	84 (28.8%)	55 (29.9%)	95 (50.0%)	< .001
No	219 (71.6%)	128 (79.5%)	208 (71.2%)	129 (70.1%)	95 (50.0%)	
History of prior prostate biopsy						
Yes	102 (33.3%)	56 (34.8%)	110 (37.7%)	73 (39.7%)	108 (56.8%)	< .001
No	204 (66.7%)	105 (65.2%)	182 (62.3%)	111 (60.3%)	82 (43.2%)	
PI-RADS score						
2	2 (0.7%)	2 (1.2%)	2 (0.7%)	1 (0.5%)	25 (13.2%)	< .001
3	58 (19.0%)	26 (16.1%)	52 (17.8%)	40 (21.7%)	34 (17.9%)	
4	159 (52.0%)	69 (42.9%)	151 (51.7%)	89 (48.4%)	66 (34.7%)	
5	81 (26.5%)	56 (34.8%)	83 (28.4%)	54 (29.3%)	57 (30.0%)	
Unknown	6 (2.0%)	8 (5.0%)	4 (1.4%)		8 (4.2%)	
No. ROI sampled						
1	243 (79.4%)	123 (76.4%)	229 (78.4%)	137 (74.5%)	146 (76.8%)	.853
2	53 (17.3%)	33 (20.5%)	52 (17.8%)	43 (23.4%)	38 (20.0%)	
3-4	10 (3.3%)	5 (3.1%)	11 (3.8%)	4 (2.2%)	6 (3.2%)	
Age, median (IQR)	66.3 (61.4-71.6)	65.3 (61.0-71.4)	66.7 (61.8-71.8)	67.7 (62.4-71.5)	66.2 (61.1-70.9)	.599
PSA, median (IQR)	7.2 (5.2-10.7)	6.9 (5.2-9.6)	6.7 (5.0-9.4)	7.0 (5.1-10.5)	6.6 (4.8-10.8)	.633
Total no. cores taken, median (IQR)	16.0 (16.0-16.0)	16.0 (16.0-18.0)	16.0 (16.0-18.0)	16.0 (16.0-18.0)	16.0 (15.0-18.0)	< .001
Average no. cores taken per ROI, median (IQR)	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (4.0-5.3)	4.0 (4.0-4.0)	3.0 (3.0-4.0)	< .001
Prostate volume, median (IQR)	47.0 (34.0-73.0)	48.7 (35.1-69.3)	47.0 (33.0-70.0)	49.0 (33.7-70.0)	47.0 (33.5-68.7)	.958
PSA density, median (IQR)	0.14 (0.09-0.24)	0.14 (0.09-0.23)	0.14 (0.10-0.21)	0.14 (0.09-0.23)	0.13 (0.09-0.20)	.738

and 4 lesions. Two providers did not meet the MUSIC quality benchmarks for cancer detection rates in PI-RADS 5 lesions.

DISCUSSION

In this study, there was no difference in CS cancer detection rates in targeted lesions across fusion biopsy providers at a single institution. Furthermore, all providers met the established MUSIC benchmark rates for CS prostate cancer in targeted cores in PI-RADS 3 and 4 lesions, while 3 out of 5 providers met the benchmark for PI-RADS 5 lesions. At the lesion level, we found no difference in CS cancer detection rates for PI-RADS 3 and 5 lesions; however, there was a statistically

Table 2. Adjusted patient-level cancer detection rate by biopsy urologist.

Urologist	No. Biopsy	Overall CDR	Targeted CDR	Standard CDR	Targeted CS CDR	Upgrading by Standard	Upgrading by Targeted	Upgrading to CS by Targeted	Upgrading to CS by Standard
A	306	90.3%	73.1%	77.7%	44.9%	22.1%	19.7%	11.2%	7.1%
B	161	81.4%	70.9%	60.8%	43.1%	13.6%	23.8%	14.6%	3.6%
C	292	85.2%	64.0%	68.4%	38.5%	23.4%	21.2%	10.2%	8.9%
D	184	83.2%	65.9%	67.2%	41.9%	21.3%	25.7%	14.3%	6.2%
E	190	83.3%	72.7%	63.7%	46.9%	17.7%	26.8%	14.7%	5.1%
P-value*		.052	.223	.005	.575	.157	.375	.439	.240

* For the comparison of CDR across urologists, based on multivariable logistic regression model controlling for age, race, family history, prostate volume, PSA, DRE, prior cancer diagnosis, number of lesions, number of cores taken, maximum PI-RADS score.

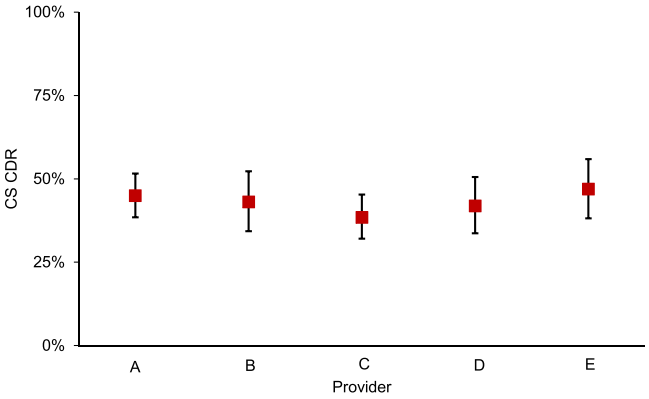

Figure 1. Targeted Clinically Significant Cancer Detection Rates (CS CDR) by Fusion Biopsy Provider, Adjusted. This figure demonstrates the average overall CS CDR on targeted cores with fusion biopsy for each provider at the single institution in our study. The error bars represent the standard error of each value based on fixed-effect logistic regression model. (Color version available online)

significant difference among PI-RADS 4 lesions across providers. In this context, the lack of a difference identified in the PI-RADS 3 and 5 subgroups may represent the known pre-test probability of CS cancer with the PI-RADS scoring system.[7,15] For example, given the high likelihood of CS prostate cancer in PI-RADS 5 lesions (70%-95%), a much larger sample size would be required to determine differences across providers if they did indeed exist. In PI-RADS 4 lesions, where there may be greater uncertainty and overlap in scoring, differences at the provider level, such as biopsy technique, may contribute to variation in cancer detection rate. Collectively, these findings suggest that, among experienced providers, variation at the provider level may contribute to differences in overall CS cancer detection rates but only within PI-RADS 4 lesions.

While our study reviewed cancer detection rates stratified by urologist, Sonn et al. reported that correlation between cancer detection and PI-RADS score varied across radiologists. Interestingly, in their adjusted model, radiologist, PI-RADS score, and history of active surveillance were associated with detection of CS prostate cancer while radiologist volume was not.[7]

Inter-reader variability in PI-RADS risk classification by experienced radiologists has recently been noted.[15-17] A retrospective review across 26 centers found the positive predictive value (PPV) of Prostate MRI is low and varies significantly across centers. Specifically, a PPV of 39% (IQR 25%-55%) was reported among 2071 PI-RADS 4 lesions.[18] Additionally, Ghabili et al. found that location, multifocality, and PI-RADS classifications of other lesions were other factors that affected CS cancer detection rates in PI-RADS 4 lesions.[19] The low PPV and variation across centers are likely multifactorial beyond radiologist interpretation. As such, the difference we identified across providers in CS cancer detection within PI-RADS 4 lesions may represent the known multifactorial variation within the PI-RADS scoring system despite similar MRI acquisition parameters in our study.

No optimal fusion biopsy technique has currently been defined. Studying the effect of specific differences in technique on variation in cancer detection rate may be beneficial but can pose a logistical challenge as technique varies not only by provider, but by lesion size, location, and anatomy. For example, larger lesions may undergo additional sampling to ensure adequate representation of the region of interest and minimize the risk of misclassification due to Gleason heterogeneity.[20] At the same time, some providers may limit cores from larger lesions due to the lower risk of registration error. Such decisions are inherently provider and patient specific. Though this was not specifically investigated in this study due to deidentification of providers, potential areas of variation in fusion biopsy technique are presented in Appendix A.

Our current study was not able to address provider-level variation by volume or whether differences exist early along the learning curve.[21,22] It is likely that nascent programs may experience suboptimal outcomes until MRI interpretation is consistently correlated with biopsy and prostatectomy pathology, to calibrate MRI interpretation and biopsy technique. Robust quality assurance programs and multidisciplinary review have been previously proposed as tools to shorten the learning curve.[13]

While several factors that drive variation in fusion biopsy have been identified in other work, our study is one of the first that has investigated variation at the urologist level.[23,24]

Table 3. Lesion-level clinically significant cancer detection rate by biopsy urologist.

	PI-RADS-3 Lesion		PI-RADS-4 Lesion		PI-RADS-5 Lesion	
	No. Lesion	CS CDR	No. Lesion	CS CDR	No. Lesion	CS CDR
Total	307	14.0%	691	36.6%	358	70.1%
Urologist						
A	79	12.7%	205	43.4%	85	63.5%
B	36	11.1%	95	35.8%	61	78.7%
C	78	16.7%	192	26.6%	90	71.1%
D	61	16.4%	111	37.8%	62	72.6%
E	53	11.3%	88	42.1%	60	66.7%
P-value*		.838		.003		.766

* For PI-RADS 3 lesions, *P*-value represents the comparison of CDR across urologists, based on Chi-squared test. For PI-RADS 4 and 5 lesions, *P*-value represents the comparison of CDR across urologists, based on multivariable logistic regression model controlling for age, race, family history, PSA, prostate volume, DRE, prior cancer diagnosis. *P*-value for PI-RADS 3 lesions is not adjusted by multivariable logistic regression because of model convergence.

Our study does have several limitations. First, it was performed at a single institution. The 5 providers were all trained in fusion biopsy in a similar setting, often disseminating knowledge and training internally, which could result in gross similarities in technique. However, discrete differences were still noted between providers. Second, this study utilized a team of 13 different radiologists for whom we were unable to adjust for in analysis due to variable volume by the radiology provider. However, these conditions accurately reflect real-world practice. Furthermore, the 5 providers in our study are high-volume fusion biopsy providers with years of experience prior to the study window. Although it is likely that these providers are beyond the learning curve of fusion biopsy, there are varying thresholds for competency in the literature.[12,25] Nevertheless, this cohort of providers represents varying levels of experience and biopsy volume. Where significant provider variation may exist is along the learning during initial startup of a fusion biopsy program. The multiple (relatively) complex steps of a fusion biopsy procedure including the sweep (US image acquisition), segmentation, co-registration, management of gland deformation, and anatomic variations that can affect image quality may considerably affect biopsy outcomes for inexperienced providers. Finally, we did not include PI-RADS 1 or 2 lesions in our study given that not all patients underwent prostate biopsy, likely introducing significant selection bias in this subset.

These limitations notwithstanding, our study has implications for quality improvement activities in fusion biopsy care for prostate cancer patients. If there is substantial variation in CS cancer detection with fusion biopsy, sources of variation such as biopsy workflow, MRI imaging quality, or variation in radiologist interpretation should also be considered. For patients, our findings suggest that, when choosing a fusion biopsy provider, providers achieve similar outcomes. Ultimately, when benchmark measures are achieved, differences across providers with access to the same supportive resources may not have a large effect on variation in overall cancer detection rates.

CONCLUSION

Fusion biopsy providers at the same institution meet acceptable cancer detection benchmarks, even when not correcting for radiologist or subtleties of biopsy technique. However, there is significant variation in CS prostate cancer detection in PI-RADS 4 lesions across urology providers at a single institution. The reasons for variation are likely multifactorial, and future work studying the role of individual provider technique and experience may help standardize procedural factors to optimize cancer detection. Understanding practice-level and radiologist-level variation will also clarify the relative impact of fusion biopsy variables on cancer detection rates. As adoption of fusion biopsy continues to grow, it will be essential to address the complex and multifactorial variation in outcomes to improve clinical care.

DECLARATION OF COMPETING INTEREST

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Appendix A. Potential areas for variation in fusion biopsy technique

1. Number of targeted cores taken at biopsy
   - o Per lesion
   - o By PI-RADS risk category
   - o By lesion size
2. Core acquisition

At centroid point or lesion mapping(1)End-fire or side-fire sampling(2)Axial or sagittal sampling(3)

1. Imaging and Co-Registration

End-fire or side-fire sweep(4)Transverse or sagittal sweep(5)Initial or Real time/continuous co-registration(6)

- o Ultrasound segmentation performed by trained medical assistant vs physician
- o Elastic or rigid registration algorithm

1. Sampling at the center of lesion or obtaining cores in different locations in the lesion volume
2. Refers to the angle of entry into the prostate of the biopsy needle with reference to the ultrasound probe. In end-fire, the tip enters without an angle. In side-fire, the tip enters at an angle.
3. During end-fire sampling, cores may be acquired in the axial or sagittal views.
4. Refers to ultrasound image acquisition to create the 3D ultrasound volume with end-fire or side-fire probe.
5. Refers to the ultrasound imaging view during ultrasound imaging acquisition to create a 3D ultrasound volume.
6. Refers to single, initial MR/US co-registration versus continuous registration to compensate for patient movement or gland deformation.

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