How I Do It – MRI-ultrasound fusion prostate biopsy using the Fusion MR and Fusion Bx systems

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There is increasing evidence to support the use of multiparametric magnetic resonance imaging (MRI) in men at risk for clinically significant prostate cancer to help identify lesions and inform biopsy. Randomized, level 1 evidence demonstrates that men who are managed with MRI and MRI-ultrasound fusion targeted biopsy (MRF-TB) have more clinically significant prostate cancer and less clinically insignificant prostate cancer detected and avoid biopsy altogether more often than men who undergo systematic, whole-gland prostate biopsy (SPB). Furthermore, strategies that incorporate MRF-TB have lower rates of upgrading on radical prostatectomy compared to SPB. However, generalizing this data to wider practice is challenging because there is a learning curve for interpreting MRI and performing MRF-TB, and some of the fusion technologies are better than others. We describe our group's early experience with the Fusion MR and Fusion Bx systems (Focal Healthcare, Toronto, ON, Canada). These products are designed with elastic fusion technology that is user-friendly, intuitive and accurate. The Fusion MR contouring system is straightforward and allows for contouring with several MRI sequences simultaneously. The Fusion Bx biopsy system has a semi-robotic arm that accounts for prostate deformation and patient movement and allows for freehand-like access, which is a seamless transition from SPB for clinicians. There were 68 lesions targeted in the first 51 patients. The overall cancer detection rate was 22%/61%/83% for PI-RADS 3/4/5, respectively. The Gleason grade group 2 prostate cancer or higher rate was 6%/47%/75% for PI-RADS 3/4/5, respectively. There were no major complications in this cohort of patients. Limitations of this study include small number of patients and lack of formal follow up to rule out sepsis. Overall, the Fusion MR and Fusion Bx systems are accurate, straightforward and safe to use for MRF-TB. Early experience does not show any significant learning curve.

Key Words: multiparametric magnetic resonance imaging, prostate cancer, systematic prostate biopsy, MRI-ultrasound fusion-targeted biopsy, Gleason grade group

Introduction

There is increasing evidence to support the use of multiparametric magnetic resonance imaging (MRI) in men at risk for clinically significant prostate cancer to help identify lesions and inform biopsy.[1] Randomized, level 1 evidence demonstrates that men who are managed with MRI and MRI-ultrasound fusion targeted biopsy (MRF-TB) have more clinically significant prostate cancer and less clinically insignificant prostate cancer detected and avoid biopsy altogether more often than men who undergo systematic, whole-gland prostate biopsy (SPB).[2] Furthermore, strategies that incorporate MRF-TB have lower rates of upgrading on radical prostatectomy compared to those using only SPB, suggesting low rates of missed clinically significant cancer in MRF-TB based strategies.[3] A recent meta-analysis looking at 29 studies and 13,845 patients confirms that MRF-TB identifies more high-grade prostate cancer than SPB.[4]

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However, generalizing this data to wider practice is challenging for several reasons. MRI interpretation, particularly in the prostate transition zone, is subject to high levels of inter-reader variability even at high-volume academic centers.[5,6] Another challenge of generalizing data from centers with high experience, is that outcomes of MRF-TB are also dependent on the technology being used and the expertise and experience of the user.[7] Herein we describe our early experience using a novel MRI contouring software application (Fusion MR) and MRI-ultrasound fusion biopsy system (Fusion Bx) that was designed to be a seamless transition for clinicians who are already performing free-hand prostate biopsy. We describe some tips and tricks for maximizing accuracy and efficiency. We also present the pathological outcomes from the first 51 patients who underwent biopsy.

Methods and technique

Patient population and biopsy setting

From April 2019 to January 2020 men with clinical suspicion of prostate cancer and at least one PI-RADS 3-5 lesion on MRI were offered MRF-TB with or without systematic biopsy. MRI is offered to men with a rising or abnormal prostate-specific antigen (PSA) for both biopsy-naïve men and men with a history of prior negative biopsy. MRI is also commonly used for men on active surveillance for localized low- and intermediate-risk prostate cancer. MRIs from outside institutions were allowed if the quality was deemed acceptable based on initial review.

Prostate and lesion contouring and prostate biopsy were carried out by one of two urologic oncologists each with significant experience with free-hand prostate biopsy and TRUS guided prostate interventions. Biopsies were performed in a medical clinic with day-case operating rooms. Fusion biopsy was carried out with 3-6 cores per target at the discretion of the treating physician. Systematic, whole-gland sampling was performed in addition to targeted biopsy for some men based on the clinical scenario for each man.

Device details

The Fusion MR and Fusion Bx systems (Focal Healthcare, Toronto, ON, Canada) were used to contour and perform the MRF-TBs. Fusion MR is a software application for interpreting MRIs of the prostate. This is the first step of an MRI-targeted biopsy procedure where lesions are identified using color-coded contours. Contoured MRIs are then transferred to the Fusion Bx, which was connected to a standard Flex Focus ultrasound and 8808e side-fire transrectal probe. The Fusion Bx uses both rigid and elastic image registration techniques to guide the physician to the lesions and has a counterbalanced semi-robotic arm that assists in the biopsy procedure by tracking all movements of the probe and keeping it steady throughout.

MR contouring

MRIs were contoured prior to prostate biopsy sessions using the Fusion MR application, Figure 1. DICOM images were uploaded to the system ensuring both T2 and diffusion weighted images (DWI) sequences were available. Other sequences can be uploaded as well. Contouring is performed in the T2 axial sequence but any other sequence can be viewed simultaneously in the three open windows to help discern lesion and prostate margins. Prostate contouring begins with confirming the slices at the extreme apex and base. Then the clinician is asked to identify the most anterior and posterior capsular prostate margin at the midgland level.

The prostate margin is then contoured on each axial slice with imputation from the software once two axial slices have been delineated. By contouring slices near the apex and base the imputation was felt to be more accurate and required less manual adjustment. The slices and contouring can be easily adjusted upon review to add precision. Once a few slices are modified, the program will impute the other slices. Comparing the sagittal view to the axial view confirms the accurate apex and base positioning. Once we are happy with the contouring, the targets are then added. The software has the ability to assign different colors to each of the targets that we define. In some patients, targets were highlighted by radiologists in saved DICOM images, but in most cases we used their reports and our interpretation of the MRI to create the targets in 2 dimensions on the T2 sequence, Figure 2.

The contours with the targets are then transferred to the Fusion Bx system.

Positioning the probe and ultrasound contouring

Patient is placed in the left side decubitus position and with TRUS guidance the prostate is anesthetized free-hand using 5 cc of local anesthetic per side. We then connect the TRUS probe to the Fusion Bx semi-robotic arm, Figure 3. It is important to ensure that the TRUS images are gated so that the entire prostate is visualized in the sagittal plane. The green button on the semi-robotic arm is then pushed by the clinician who then initiates a slow sweep of the probe in its fixed position from the right to left side of the gland to capture a 3D ultrasound volume. Performing this step slowly ensures that the entire prostate is visualized and captured.

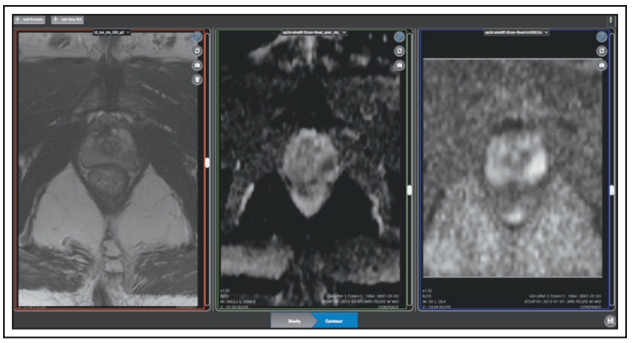

Figure 1. The Fusion MR application, displaying T2W, B1400 and ADC images.

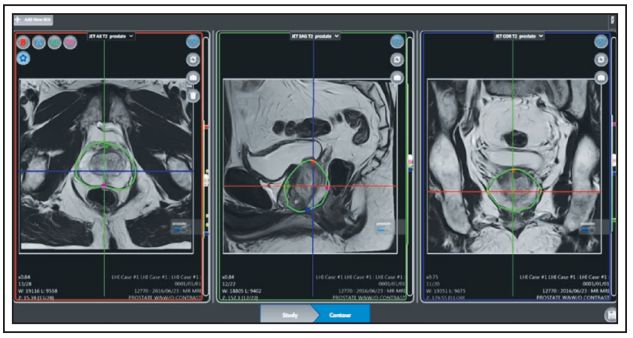

Figure 2. Axial view of the segmented prostate and lesion, contoured using the Fusion MR application.

Figure 3. The TRUS probe mounted onto the Fusion Bx semi-robotic arm.

This is an important step since the quality of the MRI-ultrasound fusion depends on having the full prostate from apex to base visualized and contoured in the MRI and ultrasound images.

The Fusion Bx system will then display sagittal and axial ultrasound images based on the 3D sweep, alongside the equivalent MRI sequences. Before proceeding with contouring, it is important to verify that all areas of the prostate, particularly the areas containing biopsy targets are well seen. If they are not, we have found that repositioning the probe, evacuating debris in the rectum by removing and then reinserting the probe and/or adding gel to the condom are all maneuvers that help to improve imaging.

For the most accurate MRI-ultrasound fusion to occur, the contoured volume on 3D ultrasound should be within 5% of the contoured MRI volume. These volumes are updated in seconds each time adjustment is made to the contouring. Smooth, accurate ultrasound contouring is best achieved by contouring on as few axial slices as possible and allowing the system to interpolate. From our experience contouring close to the apex and again close to the base is ideal. We also try to avoid manually adjusting the interpolated contours. It is best to return to a slice that has already been contoured, delete the contour and then re-do it. Once the operator is satisfied with the contours the images are fused. In addition to a standard rigid registration, Fusion Bx also does an elastic registration, which accounts for the differences in shape and size between the MRI and ultrasound volumes.

Prostate biopsy

The biopsy step of the Fusion Bx displays two simultaneous views. One is a 3D model of the prostate that shows the locations of the lesions as well as the

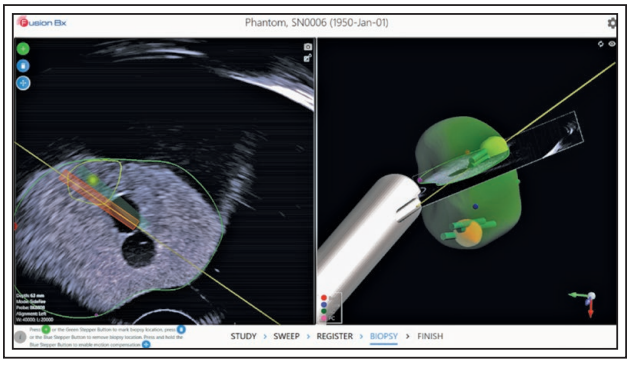

Figure 4. Fusion Bx biopsy view; showing on the left is the live ultrasound view with the contour and lesion overlay, and on the right is the 3D model of the prostate and lesions in relation to the ultrasound probe.

ultrasound probe. This makes it easy to navigate to the sagittal plane of the desired biopsy location. The second view is the live ultrasound image along with the contour (drawn in the previous step) and lesions overlaid. This allows us to visualize the needle as it enters the prostate to ensure we are on the correct trajectory, Figure 4.

Based on the shape and orientation of the lesion we adjust the semi-robotic arm so that each core will sample as much of the lesion as possible. This can be done with several maneuvers including inserting and withdrawing the probe or adjusting the angle by expanding or collapsing the arm. It is important to constantly reassess the fusion overlay. The semi-robotic arm has two independent adjustment dials. Each will allow millimeters of movement either in the lateral-medial plane or the cranial-caudal plane, to get closer to the base or the apex. These adjustments do not affect the anterior-posterior positioning of the arm. If one needs to hit an anterior or posterior target, then the arm is adjusted manually. The semi-robotic arm of the Fusion Bx is counterbalanced so that after taking our hand off the arm, the probe remains steady. This limits prostate deformation and allows for patient movement to be detected. The system will account for prostate deformation and patient movement to a degree. But if there is clear misalignment the "snap-to-home" feature allows you to recalibrate on the fly. We suggest doing this after any major adjustment in the arm or major patient movement. If it is a large target, it is important to annotate properly (i.e. base or apex of target). Multiple cores should be taken of each target. The physician will decide if all or any of the standard systematic biopsies are necessary in addition to the target. Each core location is saved in a report and sent to the patient's chart for future reference.

Adverse event monitoring

Patients were monitored for up to 1 hour following each biopsy to rule out any major, immediate adverse event. In the biopsy center, patients are recovered by registered nurses who check vital signs twice and make sure that men are able to spontaneously void prior to discharge from the clinic. During the follow up visit where pathology results are reviewed with patients, each clinician inquired about any adverse effects of the biopsy and documented any major adverse outcomes.

Data collection and statistical analysis

Clinicopathologic details and biopsy pathology outcomes were collected. MRI was reviewed for each patient including prostate volume (PV), prostate-specific antigen (PSA), PSA density (PSAD), and PI-RADS score for each lesion. When both a TRUS volume and MRI volume were available the MRI volume was used to calculate PSAD. We examined the 'any cancer detection rate' and 'clinically significant cancer rate' (defined as ≥ Gleason grade group 2 (GGG2)) per lesion and per patient. If multiple findings were identified in a single lesion, the more significant one was counted. We also explored the presence of non-cancer pathology in these lesions and clustered them into inflammation/atrophy and HGPIN categories. The association between clinical predictors and clinically significant prostate cancer was explored using univariate and multivariable comparisons. Predictors included age, PV, PSA, PSAD, and PI-RADS score in a logistic regression model. All statistics were performed using 2-sided tests with alpha < 0.05 as cut off. Statistical analysis was conducted using R-studio.

TABLE 1. **Baseline clinical characteristics of the patients in the study**

	n (51)	**%**
Age, year		
Median IQR	67 (61-70)	
< 70	36	70
≥ 70	15	30
Total PSA, ng/mL		
Median (IQR)	7.5 (5.15-10.6)	
MRI prostate volume, mL		
Median (IQR)	57 (38.50-78.50)	
PSA density (ng/mL/cc)		
Median (IQR)	0.14 (0.09-0.24)	
Number of lesions		
1 lesion	35	69
2 lesions	15	29
3 lesions	1	2
Highest PI-RADS score		
PI-RADS 3	10	20
PI-RADS 4	31	60
PI-RADS 5	10	20

TABLE 2. **Characteristics of the lesions biopsied**

	n (68)	**%**
PI-RADS score		
PI-RADS 3	18	26
PI-RADS 4	38	56
PI-RADS 5	12	18

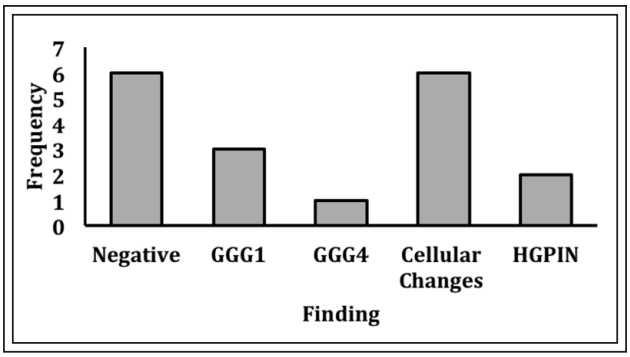

Figure 5. The distribution of findings in PI-RADS 3 lesions including high grade prostatic intraepithelial neoplasia (HGPIN), Gleason grade group (GGG) pathology and cellular changes including: inflammation, glandular atrophy and glandular hyperplasia.

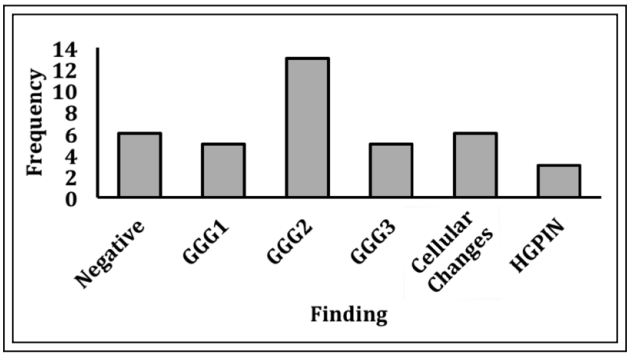

Figure 6. The distribution of findings in PI-RADS 4 lesions including high grade prostatic intraepithelial neoplasia (HGPIN), Gleason grade group (GGG) pathology and cellular changes including: inflammation, glandular atrophy and glandular hyperplasia.

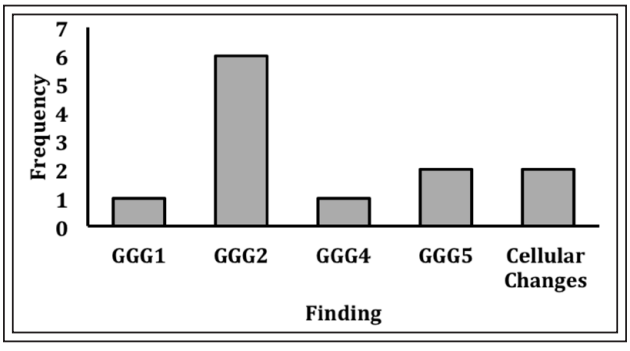

Figure 7. The distribution of findings in PI-RADS 5 lesions including high grade prostatic intraepithelial neoplasia (HGPIN), Gleason grade group (GGG) pathology and cellular changes including: inflammation, glandular atrophy and glandular hyperplasia.

Results

There were 51 patients with 68 lesions included in this study. The median age of the patients was 67 years (interquartile range [IQR]: 61-70). The median level of serum PSA and PV were 7.5 ng/mL (IQR: 5.15-10.6) and 57 mL (IQR: 38.50-78.50), respectively. While the majority of patients had a single lesion (69%), 15 men had two lesions (29%) and 1 man had three lesions (2%). Clinical, serological and MRI results are presented in Table 1. The distribution of pathologic findings per lesion is presented in Table 2 and Figures 5-7. MRF-TB results that detected any pathology (cellular changes or prostate cancer) in the lesions were 67%/84%/100% for PI-RADS 3/4/5 respectively. The any cancer detection rate is 22%/61%/83% for PI-RADS 3/4/5 respectively and the GGG2 or greater rate is 6%/47%/75% for PI-RADS 3/4/5 respectively.

The results of the univariate and multivariate logistic regression are shown in Tables 3 and 4. Univariate analysis demonstrated that PSAD (ng/dL/cc), MRI PI-RADS score of 5 and prostate volume (mL) were significant predictors of identifying any prostate cancer, as well as clinically significant cancer (≥ GGG2) (each $p < 0.05$). Moreover, PSAD was found to be a significant predictor of clinically significant cancer.

On multivariable analysis, PI-RADS 4 ($p = 0.033$) and PI-RADS 5 ($p = 0.021$) were significant predictors of finding any prostate cancer on biopsy. Furthermore, PI-RADS 4 ($p = 0.023$) and PI-RADS 5 ($p = 0.005$) and age ($p = 0.047$) were significant predictors of finding a clinically significant cancer.

There were no significant adverse events on the day of biopsy or within 6 weeks of biopsy at time of pathology review

Discussion

In this manuscript we highlight the workflow for contouring prostate MRI lesions and performing targeted biopsies using the novel Fusion MR and Fusion Bx systems. There is a relatively short learning curve with this particular platform. We believe that the flexible semi-robotic arm allows for very precise and reproducible biopsy targeting, which is not lost after each core is taken. The software can be uploaded to almost any computer, so that the physician can do the contouring and targeting at their leisure. Then using a flash drive, the images can be uploaded to the Fusion Bx system. The Fusion Bx is compatible with any ultrasound machine with a video output, and can be adapted to fit any ultrasound probe using a unique

TABLE 3. **Univariate and multivariate logistic regression results exploring the association between various predictors and the identification of any prostate cancer on targeted biopsy.**

Predictor	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
PSA density (ng/dL/cc)	1.11	1.03, 1.21	0.014	1.05	0.92, 1.27	0.5
Number of lesions with PI-RADS ≥ 3	1.24	0.41, 4.04	0.7	0.54	0.12, 2.28	0.4
Highest PI-RADS						
3	---	---	---	---	---	---
4	3.69	0.85, 19.8	0.095	8.10	1.34, 68.5	0.033
5	21.0	2.41, 492	0.016	30.5	2.35, 1042	0.021
Age, year	1.06	0.98, 1.15	0.2	1.08	0.97, 1.23	0.2
Prostate volume (mL)	0.98	0.96, 0.99	0.024	0.98	0.94, 1.01	0.2
PSA (ng/mL)	1.05	0.98, 1.18	0.3	1.04	0.77, 1.42	0.8

probe cradle that latches onto the handle. Moreover, both transrectal and transperineal approaches can be accommodated with the same setup.

The cancer detection rate stratified by PI-RADS score is in keeping or even slightly higher than the published literature. For example, Mehralivand et al looked at their experience with 339 patients at the NIH going for MRI-ultrasound fusion biopsy using UroNav Platform (Invivo).[8] They found that clinically significant prostate cancer was found in 13%/23%/76% of PI-RADS 3/4/5, respectively. This was from a center with significant experience in both MRI interpretation and transrectal MRI-ultrasound fusion biopsy. The median PSA for their patients was 6.5 and ours was 7.5. Thus, accounting for the slightly different patient populations, our outcomes in the first 51 patients approximates that of a high-volume center.

Our data reflects a "real-world" experience and is, therefore, perhaps more generalizable than other publications. Many of the MRIs and radiology reports that we used to plan biopsies were from non-academic, low-prostate volume centers. Despite this, the accuracy of the device in finding any pathology in the lesions was extraordinarily high (67% PI-RADS 3, 84% PI-RADS 4, 100% PI-RADS 5).

There are several limitations in this project. First, the sample size is small, thus there is room for type 1 errors. Furthermore, there is no comparison made between fusion and systematic samples. This was omitted because many patients had fusion only and the indications for systematic and number of systematic cores varied dramatically.

In summary, we feel that the Fusion MR and Fusion Bx systems use intuitive workflows that are simple and

TABLE 4. **Univariate and multivariate logistic regression results exploring the association between various predictors and the identification of clinically significant prostate cancer (≥ Gleason grade group 2) on targeted biopsy.**

Predictor	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
PSA density (ng/dL/cc)	1.07	1.02, 1.15	0.026	0.99	0.87, 1.16	> 0.9
Number of lesions with PI-RADS ≥ 3	1.11	0.37, 3.30	0.9	0.54	0.12, 2.13	0.4
Highest PI-RADS						
3	---	---	---	---	---	---
4	7.41	1.18, 145	0.072	19.5	2.13, 501	0.023
5	36.0	3.79, 928	0.007	127	6.71, 7130	0.005
Age, year	1.07	0.99, 1.18	0.11	1.14	1.01, 1.33	0.047
Prostate volume (mL)	0.98	0.95, 0.99	0.030	0.96	0.90, 1.00	0.7
PSA (ng/mL)	1.05	0.98, 1.15	0.2	1.05	0.79, 1.46	0.8

aptly designed for clinicians experienced in free-hand prostate biopsy. Using some of the tips and tricks described in the methods section we believe that our workflow and results can be approximated in most centers with minimal infrastructure change.

Disclosures

The authors have no disclosures. □

References

1. Siddiqui MM, Rais-Bahrami S, Turkbey B et al. Comparison of MR/ultrasound fusion–guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015;313(4):390-397.
2. Kasivisvanathan V, Rannikko AS, Borghi M et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378(19):1767-1777.
3. Ahdoot M, Wilbur AR, Reese SE et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl J Med* 2020;382(10):917-928.
4. Goldberg H, Ahmad AE, Chandrasekar T et al. Comparison of MRI-and TRUS-informed prostate biopsy for prostate cancer diagnosis in biopsy-naive men: a systematic review and meta-analysis. *J Urol* 2019 Oct 11:10-97.
5. Pickersgill NA, Vetter JM, Andriole GL et al. Accuracy and variability of prostate multiparametric magnetic resonance imaging interpretation using the Prostate Imaging Reporting and Data System: a blinded comparison of radiologists. *Eur Urol Focus* 2020;6(2):267-272.
6. Greer MD, Shih JH, Lay N et al. Interreader variability of prostate imaging reporting and data system version 2 in detecting and assessing prostate cancer lesions at prostate MRI. *AJR Am J Roentgenol* 2019;212(6):1197-1205.
7. Wegelin O, van Melick HH, Hooft L et al. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: a systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? *Eur Urol* 2017;71(4):517-531.
8. Mehralivand S, Bednarova S, Shih JH et al. Prospective evaluation of PI-RADS™ version 2 using the international society of urological pathology prostate cancer grade group system. *J Urol* 2017;198(3):583-590.