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Clinical-Prostate cancer

The effect of delaying transperineal fusion biopsy of the prostate for patients with suspicious MRI findings—Implications for the COVID-19 era

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Abstract

Objective: Image guided biopsies are an integral part of prostate cancer evaluation. The effect of delaying biopsies of suspicious prostate mpMRI lesions is uncertain and clinically relevant during the COVID-19 crisis.

We evaluated the association between biopsy delay time and pathologic findings on subsequent prostate biopsy.

Materials and methods: After obtaining IRB approval we reviewed the medical records of 214 patients who underwent image-guided transperineal fusion biopsy of the prostate biopsy between 2017 and 2019.

Study outcomes included clinically significant (ISUP grade group ≥2) and any prostate cancer on biopsy. Logistic regression was used to evaluate the association between biopsy delay time and outcomes while adjusting for known predictors of cancer on biopsy.

Results: The study cohort included 195 men with a median age of 68. Median delay between mpMRI and biopsy was 5 months, and 90% of patients had a ≤8 months delay. A significant association was found between PI-RADS 5 lesions and no previous biopsies and shorter delay time.

Delay time was not associated with clinically significant or any cancer on biopsy. A higher risk of significant cancer was associated with older age ($P = 0.008$), higher PSA (0.003), smaller prostate volume (<0.001), no previous biopsy (0.012) and PI-RADS 5 lesions (0.015).

Conclusions: Our findings suggest that under current practice, where men with PI-RADS 5 lesions and no previous biopsies undergo earlier evaluation, a delay of up to 8 months between imaging and biopsy does not affect biopsy findings.

In the current COVID-19 crisis, selectively delaying image-guided prostate biopsies is unlikely to result in a higher rate of significant cancer.

Keywords: Image guided prostate biopsy; Magnetic resonance imaging; Prostate cancer; Treatment delay

1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) of the prostate and image guided prostate biopsies are evolving as an integral part of the evaluation and diagnosis of prostate cancer [1]. Randomized prospective trials suggest that performing mpMRI prior to prostate biopsy and combining targeted and systematic biopsies may improve the detection of clinically significant prostate cancers and lower the rate of tumor upgrading at radical prostatectomy [2−4].

When treating prostate cancer, a delay between biopsy and treatment most likely does not affect outcome in patients with low-risk disease. However, treatment delay might have a deleterious effect in high-risk patients [5−7]. To the best of our knowledge it is unclear whether delaying

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prostate biopsies from the time of identifying a suspicious prostate lesion on mpMRI affects biopsy findings.

The current coronavirus disease 2019 (COVID-19) pandemic has led to major healthcare system changes with the aim of containing the viral spread and treating patients requiring critical care [8]. Consequently, new considerations are taken into account when prioritizing patients for urological procedures leading to treatment delay even among cancer patients [9−14]. Given current concerns regarding treatment delay due to the COVID-19 pandemic, we aimed to evaluate the association between biopsy delay time after identifying an mpMRI lesion suspicious for prostate cancer and pathologic findings on subsequent image-guided transperineal fusion biopsies of the prostate.

2. Materials and methods

After obtaining institutional review board approval we reviewed the medical records of 214 patients who underwent mpMRI guided transperineal fusion biopsy of the prostate between May 2017 and September 2019 at our institution, a public health system tertiary care center. Five patients who had their MRI performed with a 1.5-Tesla machine and 2 patients whose imaging studies were not available for review were excluded. We also excluded 12 patients who had their biopsy performed over 1 year from the date of imaging to avoid outliers with substantially long biopsy delay time, leaving a total of 195 patients for further analyses.

All patients included in the study cohort underwent an evaluation for prostate cancer due to an elevated serum prostate specific antigen (PSA) level and/ or an abnormal digital rectal exam (DRE). Baseline clinical characteristics of the study cohort including age, PSA value (ng/mL), clinical tumor stage and prior biopsies were collected from the patients' medical records. Prior to their biopsy, the patients underwent a 3-Tesla mpMRI without an endorectal coil. T_2-weighted, contrast-enhanced, and diffusion-weighted series were obtained and mpMRI lesions were given a Prostate Imaging Reporting and Data System (PI-RADS) v2 score of 1 to 5 to stratify the risk of prostate cancer [15]. The mpMRI images were reviewed and annotated by a senior genitourinary radiologist (SB). All men had at least one PI-RADS ≥3 lesion on imaging. Prostate volume (cm^3), number of lesions and maximal PI-RADS score were collected.

Patients underwent an mpMRI-transrectal ultrasound (TRUS) fusion guided transperineal prostate biopsy, performed by 1 of 3 senior urologists (GKP, HM, and NJM), all of whom had previous experience with the procedure. The procedure was performed under general anesthesia and intravenous antibiotic prophylaxis with the patient in the lithotomy position. After the insertion of a urethral catheter, a bi-planar TRUS probe (BK Medical, Peabody MA) mounted on a flexible arm (D&K Technologies GmbH, Barum, Germany) was inserted and the prostate was visualized in the sagittal and axial planes. Rigid fusion between the mpMRI and the TRUS images was performed using the BioJet system (D&K Technologies GmbH, Barum, Germany) after outlining the contour of the prostate and the suspected lesions on the mpMRI. Software-based fusion biopsies were obtained transperineally using a 5-mm brachytherapy grid while directing the needle toward the lesion displayed on the BioJet computer screen system. A minimum of 2 cores were obtained from each target lesion after which systematic biopsies were obtained from the peripheral zone, anterior zone and apex. All biopsy specimens were reviewed by a dedicated genitourinary pathologist (GG). Each core was assessed for the International Society of Urological Pathology (ISUP) grade group [16], and a maximal grade group was assigned separately for the targeted and systematic biopsies. Significant cancer was defined when the ISUP grade group was ≥2. Pathology reports of patients diagnosed with prostate cancer who underwent radical prostatectomy were reviewed for ISUP grade group, extracapsular extension, seminal vesicle invasion, surgical margin status, and tumor stage.

Study outcomes included a finding of significant cancer and any cancer on biopsy. Patient and tumor characteristics were compared between patients with biopsy delay ≤3 months and >3 months using the rank-sum and chi-squared tests, and with biopsy delay time as a continuous variable using univariable linear regression analyses. The cut-off point of 3 months was chosen since the MRI-FIRST prospective study evaluating the role of systematic and targeted biopsies had all biopsies performed within 3 months of the mpMRI [4]. Logistic regression analyses were used to evaluate the association between biopsy delay time and the study outcomes while adjusting for previously reported predictors of cancer on biopsy including age, PSA value, previous biopsy, prostate volume, and maximal PI-RADS score on imaging. All statistical analyses were 2-sided, and significance was defined as $P < 0.05$. All analyses were conducted using R Statistical Software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The study cohort included a total of 195 men with a median age of 68 (IQR 64, 72). Baseline characteristics and imaging results of the study cohort categorized by biopsy delay time ≤3 months ($n = 59$) and >3 months ($n = 136$) are reported in Table 1. Median PSA value was 6.9 ng/ml (IQR 5.5, 10) and most patients had clinical stage T1c disease (145 patients, 77%). A higher rate of biopsy naïve patients underwent early biopsies (51% vs. 30%, $P = 0.009$). Among the 29 early biopsy patients who underwent a previous biopsy 18/29 had a negative biopsy and 11/29 had a positive biopsy and were on active surveillance. In the late biopsy group 71/95 had a negative biopsy and 24/95 had a positive biopsy. All patients had suspicious mpMRI lesions, 114 of whom (59%) had multiple lesions. Patients who underwent

Table 1
Baseline clinical characteristics and magnetic resonance imaging findings of the study cohort stratified by time to biopsy ($n = 195$); continuous variables are reported as median [IQR] and categorical variables as number (%)

Variable		Early biopsy (≤3 months) $n = 59$	Late biopsy (>3 months) $n = 136$	P value
Age (years)		67 [62, 72]	68 [64, 72]	0.26
PSA (ng/dL)		6.9 [5.7, 10.4]	7 [5.5, 9.8]	0.54
Clinical stage ($n = 189$)	T1c	46 (82)	99 (74)	0.55
	T2a	7 (13)	27 (20)	
	T2b	3 (5)	4 (3)	
	T2c	0 (0)	2 (2)	
	T3	0 (0)	1 (1)	
Previous biopsy	No	30 (51)	41 (30)	0.009
	Yes	29 (49)	95 (70)	
Prostate volume (cm^3, $n = 183$)		60 [48, 78]	60 [37, 88]	0.77
Number of lesions		2 [1, 2]	2 [1, 2]	0.3
Multiple lesions	No	23 (39)	58 (43)	0.75
	Yes	36 (61)	78 (57)	
Maximal PI-RADS score	3	9 (15)	31 (23)	0.007
	4	31 (53)	88 (65)	
	5	19 (32)	17 (12)	

IQR = interquartile range; PSA = prostate specific antigen; PI-RADS = Prostate Imaging−Reporting and Data System.

early biopsies had a significantly higher rate of PI-RADS 5 lesion (32% vs. 13%, $P = 0.007$). When delay time was evaluated as a continuous variable, PI-RADS 5 lesions (β= -1.77, $P = 0.003$) were associated with shorter biopsy delay time and previous biopsies ($\beta = 0.93$, $P = 0.017$) were associated with longer delay time (Supplementary Table 1).

Biopsy data and results are summarized in Table 2. Biopsy findings stratified by biopsy type (systematic,

Table 2
Biopsy findings of the study cohort stratified by time to biopsy ($n = 195$); continuous variables are reported as median [IQR] and categorical variables as number (%)

Variable		Early biopsy (≤3 months) $n = 59$	Late biopsy (>3 months) $n = 136$	P value
Number of cores ROI		10 [7, 13]	9 [6, 11]	0.15
Number of positive cores ROI		1 [0, 4]	0 [0, 2]	0.12
ISUP grade group ROI	0	27 (46)	73 (54)	0.66
	1	20 (34)	33 (24)	
	2	8 (14)	20 (15)	
	3	3 (5)	4 (3)	
	4	1 (2)	5 (4)	
	5	0 (0)	1 (1)	
Number of cores systematic		20 [19, 23]	21 [19, 23]	0.23
Number of positive cores systematic		1 [0, 3]	0 [0, 2]	0.06
ISUP grade group systematic	0	23 (39)	71 (52)	0.45
	1	26 (44)	43 (32)	
	2	7 (12)	12 (9)	
	3	2 (3)	4 (3)	
	4	1 (2)	5 (4)	
	5	0 (0)	1 (1)	
Number of cores combined		30 [27, 35]	30 [26, 33]	0.8
Number of positive cores combined		2 [0, 7]	1 [0, 5]	0.06
ISUP grade group combined	0	19 (32)	58 (43)	0.19
	1	25 (42)	40 (29)	
	2	10 (17)	27 (20)	
	3	4 (7)	3 (2)	
	4	1 (2)	7 (5)	
	5	0 (0)	1 (1)	

IQR = interquartile range; ISUP = International Society of Urological Pathology; ROI = region of interest.

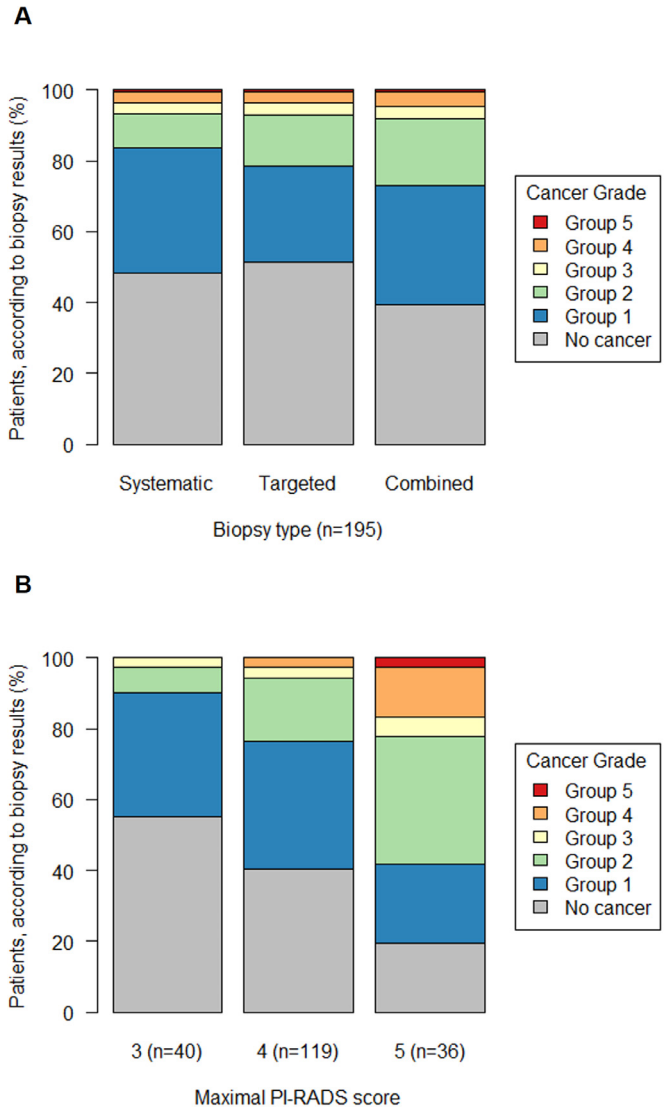

Fig. 1. Highest grade of prostate cancer detected in patients undergoing prostate biopsy ($n = 195$) categorized by (A) biopsy type – systematic, targeted and combined and (B) Maximal PI-RADS score on prebiopsy multiparametric MRI.

targeted, and combined) and by maximal PI-RADS score on prebiopsy mpMRI are shown in Fig. 1A and B, respectively. When using a combination of targeted and systematic biopsies 118/195 patients (61%) were found to have any prostate cancer and 53/195 patients (27%) were found to have clinically significant prostate cancer. When comparing targeted and systematic biopsies, targeted biopsies were associated with a higher rate of clinically significant cancer (22% vs. 16%) and a lower rate of clinically insignificant cancer (27% vs. 35%), however this did not reach statistical significance. Median number of positive cores in the combined biopsy was higher in patients undergoing early biopsy 2 (IQR 0, 7) compared to 1 (IQR 0, 5) among patients with a late biopsy ($P = 0.06$), while the total number of cores obtained did not differ significantly ($P = 0.8$).

Median delay between mpMRI and biopsy was 5 months (IQR 3, 6) and 176/195 patients (90%) underwent biopsy within 8 months of imaging. A histogram of the time interval between mpMRI and prostate biopsy is presented in Fig. 2A. Biopsy delay time was not different between patients without cancer, with insignificant cancer and with significant cancer on combined biopsy ($P = 0.14$, Fig. 2B). On multivariable logistic regression analyses biopsy delay time was not associated with the outcomes of significant or any cancer when evaluating combined biopsies or targeted and systematic biopsies separately (Table 3, Supplementary Table 2). Risk of significant cancer was associated with patient age (OR=1.11; 95% CI 1.03, 1.21; $P = 0.008$), PSA level (OR=1.12; 95% CI 1.05, 1.22; $P = 0.003$), positive previous biopsy (OR = 0.32, 95% CI 0.13, 0.77, $P = 0.012$), prostate volume (OR = 0.67; 95% CI 0.55, 0.79; $P < 0.001$) and PI-RADS 5 lesions (OR = 7.82; 95% CI 1.65, 47.78; $P = 0.015$). Age, PSA, previous biopsy, and prostate volume were also associated with the finding of any cancer on

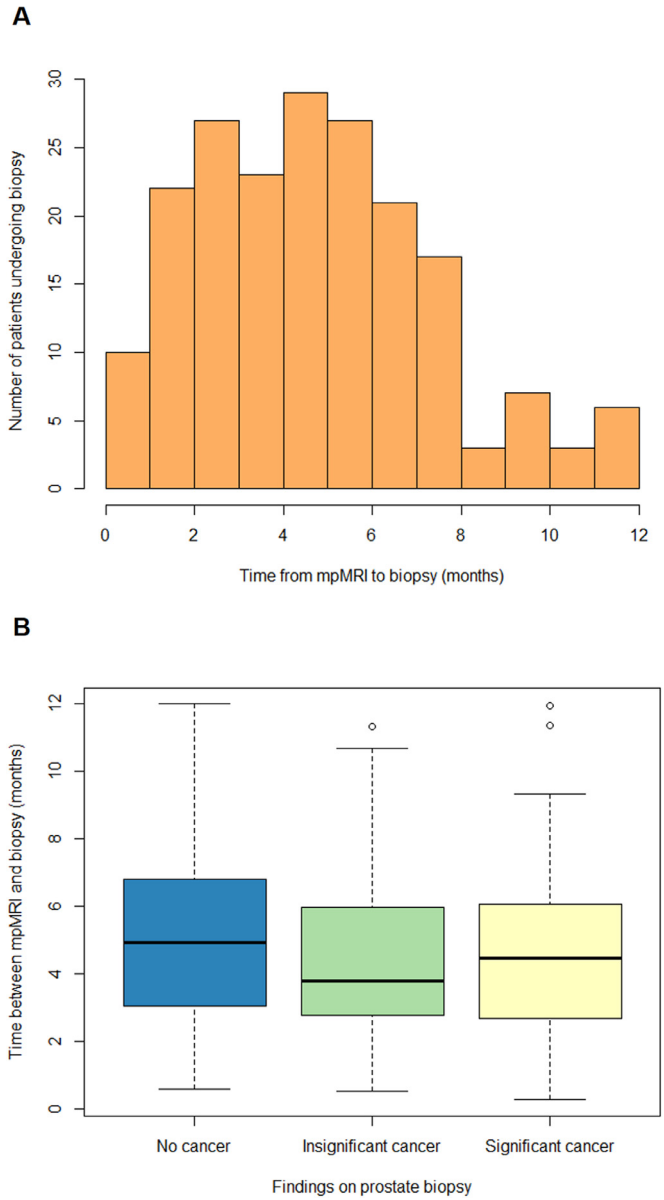

Fig. 2. (A) Histogram of time interval between multiparametric MRI and prostate biopsy in patients who underwent a biopsy within 1 year of the imaging study ($n = 195$) and (B) Box-plot chart of biopsy delay time categorized by patients without evidence of cancer, with nonsignificant cancer and with significant cancer on biopsy.

combined biopsies (Table 3). Similar associations between age, PSA value, prostate volume, and PI-RADS 5 lesions were observed when evaluating the image guided and systematic parts of the biopsy separately. Previous biopsies were associated with outcomes in the targeted but not the systematic part of the biopsy (Supplementary Table 2).

A small group of patients among those diagnosed with prostate cancer underwent radical prostatectomy (26/118, 22%). Within this group, patients with a shorter biopsy delay time (≤3 months, $n = 13$) had higher ISUP grade groups on biopsy and underwent prostatectomy earlier. Nevertheless, we did not find a significant difference in the pathologic variables at the time of prostatectomy between both groups (Supplementary Table 3).

4. Discussion

In the current study we evaluated the association between biopsy delay from the time of mpMRI and findings of significant and any prostate cancer on transperineal image guided fusion biopsies. We found that biopsy naïve patients and those with a PI-RADS 5 lesion were likely to undergo early biopsies and that under current practice, delaying a biopsy for up to 8 months was not associated with findings of significant or any cancer on combined, targeted, and systemic biopsies of the prostate. Furthermore, our findings support the association between age, PSA, previous biopsy, prostate volume, and MRI PI-RADS score with pathologic findings on biopsy.

Table 3
Multivariable logistic regression models for clinically significant prostate cancer and any prostate cancer in combined targeted and systematic biopsies of the study cohort ($n = 183$)

Variable	Significant cancer			Any cancer		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Biopsy delay time (per 1 month)	1.04	0.88, 1.23	0.62	0.91	0.79, 1.05	0.2
Age (per 1 year)	1.11	1.03, 1.21	0.008	1.13	1.06, 1.21	0.001
PSA (per 1 ng/dL)	1.12	1.05, 1.22	0.003	1.08	1.01, 1.17	0.05
Previous biopsy						
No	Ref			Ref		
Yes	0.32	0.13, 0.77	0.012	0.39	0.17, 0.87	0.023
Prostate volume (per 10 cm^3)	0.67	0.55, 0.79	<0.001	0.71	0.62, 0.81	<0.001
Maximal PI-RADS score						
3	Ref			Ref		
4	2.31	0.62, 11.96	0.26	0.99	0.4, 2.38	0.98
5	7.82	1.65, 47.78	0.015	2.45	0.63, 10.43	0.21

CI = confidence interval; OR = odds ratio; PSA = prostate specific antigen; PI-RADS = Prostate Imaging−Reporting and Data System; ref = reference value.

Prospective randomized trials have shown the benefit of using mpMRI prior to biopsy and support the role of combining systematic and mpMRI guided biopsies [2−4]. Detection rates of significant cancer in patients who underwent image guided biopsy ranged from 32% to 38%. Detection rates of clinically insignificant cancer was lower in mpMRI guided biopsy. Moreover, overall detection rate was improved by combining both techniques each of which showed substantial added value [2−4]. In the current study, when using combined biopsies, we found a 61% rate of any cancer and 27% rate of clinically significant prostate cancer, comparable to those previously reported. We also found an association between age, PSA level, previous prostate biopsies, prostate volume, MRI findings, and the detection of prostate cancer. This is consistent with a previous study by Rais-Baharmi et al. which reported older age, higher PSA value, lower prostate volume, and higher MRI suspicion score were associated with the finding of prostate cancer on biopsy [17].

Most studies evaluating the effect of treatment delay in patients diagnosed with prostate cancer do not seem to show an effect on treatment outcome, especially in low-risk patients most of whom are suitable for active surveillance [5−7]. However, in a systematic review of the literature which included 17 studies evaluating the delay between diagnosis and radical local treatment, 2 studies evaluating patients with higher-risk prostate cancer found a 2.5 to 9 months delay in treatment was associated with an increase in biochemical recurrence rate. Thus, a delay of several months or even years in definitive therapy for men with low-risk prostate cancer is unlikely to have a deleterious effect on outcome, however, for patients with high- or even intermediate-risk disease, limited data suggest that treatment beyond 3 months may compromise outcomes [7]. To the best of our knowledge no previous study evaluated whether delaying fusion biopsies from the time a suspicious lesion is found on mpMRI affects biopsy findings. In our institute, a public health system tertiary referral center, waiting times between mpMRI and fusion prostate biopsy are over 5 months in half the patients, enabling us to evaluate the effect of biopsy delay time. Our findings suggest that using our current practice, a delay of up to 8 months in prostate biopsy may not affect the rate of significant cancer or any cancer on biopsy. However, there was an association between early biopsies (≤3 months) and a higher number of positive cores despite a lack of difference in the total number of cores obtained. This result is likely related to the higher rate of PI-RADS 5 lesions in men that underwent early biopsy.

The current COVID-19 pandemic is affecting healthcare systems around the world stressing them beyond their usual capacity. The high rate of patients with severe infection which require intensive care level treatment and ventilation support has required diverting personnel and equipment to treat the crisis, limiting elective surgical cases [18]. Furthermore, when considering surgical procedures, recent evidence from Wuhan reported a 44% intensive care unit admission rate and a 20% mortality rate in asymptomatic patients who tested COVID positive after a variety of surgical procedure [19]. Additionally, there is concern about dissemination of the virus in surgical smoke particles which are abundant in laparoscopic and robotic assisted laparoscopic surgeries [20]. Subsequently, international urologic associations and various centers have suggested different strategies to prioritize urologic surgeries and office based procedures within this setting [10−14]. With regards to the diagnostic evaluation of patients suspected to have prostate cancer, Katz et al. recommend that for patients with predictors of high-risk prostate cancer (PSA > 20, rapid PSA doubling time <6 months, T3 disease on DRE and/or local or systemic symptoms) an attempt should be made to obtain an mpMRI, biopsy should be delayed up to 3 months and if performed, a transperineal approach should be preferred to limit risk of infection. For patients without

high risk factors or those undergoing biopsy as part of their active surveillance protocol, the biopsy should be delayed by up to 6 months [10]. Similarly, The European Urologic Association Guideline Office Rapid Reaction Group suggested that for patients with a PSA <10 ng/ml and without findings on DRE, an upfront mpMRI should be done prior to biopsy if possible, otherwise the biopsy should be deferred. On the other hand, for patients with a PSA > 10 ng/ml or abnormal DRE performing an upfront prebiopsy mpMRI is recommended, however if an mpMRI is not available biopsy should be performed without image guidance within 3 to 4 months or within 6 weeks if locally advanced and highly symptomatic [14]. Our findings support these recommendations, however, the association between PI-RADS 5 lesions and short delay time, as well as the high risk of significant cancer in patient with PI-RADS 5 lesions, suggest that even in the current pandemic, patients who undergo mpMRI with a PI-RADS 5 lesions should be considered for further testing with an intermediate priority.

The limitations of our study are inherent to its retrospective nature. Multiple causes may have led to the delay between mpMRI and prostate biopsy; however, within the current cohort we were unable to accurately define the cause of delay for each patient. Furthermore, while we controlled for prebiopsy baseline predictors, we may have not been able to account for all factors which led to a biopsy delay; however, it is unlikely a prospective study will evaluate the effect of delaying biopsy on findings. In the current study we did not evaluate PSA derivatives or other prebiopsy assays which may have increased the specificity of cancer detection and aided in deciding which biopsies may be delayed. Finally, only a small number of patients underwent radical prostatectomy and we did not have sufficient follow up regarding treatment outcome, precluding us from evaluating the effect of biopsy delay time on adverse pathology at prostatectomy and oncologic outcome.

5. Conclusion

Our findings suggest that under current practice, where men with PI-RADS 5 lesions and no previous biopsies undergo earlier evaluation, a delay time of up to 8 months between imaging and biopsy does not affect subsequent findings.

Within the context of the current COVID-19 crisis, and suggested changes to practice guidelines, the study findings imply that adopting a practice pattern in which fusion biopsy is selectively delayed for patients who undergo mpMRI and do not have PI-RADS 5 lesions is unlikely to lead to deleterious biopsy results.

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Conflict of Interest

All authors declare that they have nothing to disclose.

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Supplementary materials

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