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ORIGINAL ARTICLE

Prostate Cancer

Can we omit systematic biopsies in patients undergoing MRI fusion-targeted prostate biopsies?

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Magnetic resonance imaging (MRI)-targeted prostate biopsy is the recommended investigation in men with suspicious lesion(s) on MRI. The role of concurrent systematic in addition to targeted biopsies is currently unclear. Using our prospectively maintained database, we identified men with at least one Prostate Imaging-Reporting and Data System (PI-RADS) ≥3 lesion who underwent targeted and/or systematic biopsies from May 2016 to May 2020. Clinically significant prostate cancer (csPCa) was defined as any Gleason grade group ≥2 cancer. Of 545 patients who underwent MRI fusion-targeted biopsy, 222 (40.7%) were biopsy naïve, 247 (45.3%) had previous prostate biopsy(s), and 76 (13.9%) had known prostate cancer undergoing active surveillance. Prostate cancer was more commonly found in biopsy-naïve men (63.5%) and those on active surveillance (68.4%) compared to those who had previous biopsies (35.2%; both $P < 0.001$). Systematic biopsies provided an incremental 10.4% detection of csPCa among biopsy-naïve patients, versus an incremental 2.4% among those who had prior negative biopsies. Multivariable regression found age (odds ratio [OR] = 1.03, $P = 0.03$), prostate-specific antigen (PSA) density ≥0.15 ng ml^{-2} (OR = 3.24, $P < 0.001$), prostate health index (PHI) ≥35 (OR = 2.43, $P = 0.006$), higher PI-RADS score (*vs* PI-RADS 3; OR = 4.59 for PI-RADS 4, and OR = 9.91 for PI-RADS 5; both $P < 0.001$) and target lesion volume-to-prostate volume ratio ≥0.10 (OR = 5.26, $P = 0.013$) were significantly associated with csPCa detection on targeted biopsy. In conclusion, for men undergoing MRI fusion-targeted prostate biopsies, systematic biopsies should not be omitted given its incremental value to targeted biopsies alone. The factors such as PSA density ≥0.15 ng ml^{-2}, PHI ≥35, higher PI-RADS score, and target lesion volume-to-prostate volume ratio ≥0.10 can help identify men at higher risk of csPCa.

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INTRODUCTION

Prostate cancer is becoming more common in Singapore, with age-standardized incidence rates rising from 13.8 per 100 000 population in 1993–1997, to 24.2 per 100 000 population in 2003–2007, to 31.8 per 100 000 population in 2013–2017 according to the latest statistics published by the Singapore Cancer Registry, with an annual percentage increase of 4.9% from 1968 to 2017.[1]

The diagnosis of prostate cancer has traditionally been achieved histologically via transrectal ultrasound (TRUS)-guided prostate biopsy utilizing a 10–12-core systematic approach. However, the advent of multi-parametric magnetic resonance imaging (mpMRI) around 2007 has allowed urologists to better visualize any suspicious areas in the prostate gland, prior to performing a more targeted biopsy to improve diagnostic yield. Three landmark multicenter prospective trials, namely the Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not (PRECISION) trial,[2] the MRI-FIRST trial[3] and the Met Prostaat MRI Meer Mans (4M) trial[4] had shown that MRI-targeted biopsies significantly outperform systematic biopsy for the detection of clinically significant prostate cancer (csPCa - commonly defined as International Society of Urological Pathology [ISUP] grade ≥2) in the biopsy-naïve setting.

However, the role of concurrent systematic biopsies in addition to targeted biopsies is currently unclear. The 2020 European Association of Urology (EAU) guidelines recommend that for biopsy-naïve patients, when the mpMRI is positive (*i.e.*, Prostate Imaging-Reporting and Data System [PI-RADS] ≥ 3), targeted and systematic biopsy is strongly recommended. For patients with prior negative biopsy, there is a weak recommendation to perform targeted-only biopsy when the mpMRI is positive. While numerous studies have shown a substantial proportion of csPCa being missed on targeted biopsy alone, some have also reported limited additional value for systematic biopsy.[5] As such, our study aims to review our prospective series of MRI fusion targeted and systematic prostate biopsies, evaluating prostate cancer detection rates. We also evaluated whether other variables like prostate-specific antigen (PSA) density or prostate health index (PHI) could help improve the detection of csPCa.

PATIENTS AND METHODS

Patients

Consecutive patients were registered into a prospective institution review board-approved database (DSRB 2015/01252) assessing

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MRI-targeted prostate biopsy at our institution, Tan Tock Seng Hospital in Singapore. For this study, we reviewed patients who underwent biopsy from May 1, 2016, to May 31, 2020. The inclusion criteria for our study were patients with at least one PI-RADS ≥3 lesion and who underwent targeted and/or systematic biopsies. All of these patients had either a raised serum PSA and/or suspicious digital rectal examination and/or previous negative systematic TRUS-guided prostate biopsy. Our patients with total PSA between 4 ng ml^{-1} and 10 ng ml^{-1} are offered the option of PHI[6] to aid our risk stratification to predict prostate cancer[7] and counsel for/against further investigations.[8] Our institution's protocol is summarized in a patient selection flow diagram (**Figure 1**). Additionally, we also included patients with known prostate cancer on active surveillance. We defined csPCa as any ISUP grade group (GG) ≥2 cancers (previously known as Gleason score ≥7).

Details of mpMRI

All patients underwent mpMRI in accordance with PI-RADS version 2 recommendations.[9] All scans were performed on a 3-Tesla MR scanner (TrioTIM, Siemens Healthcare, Malvern, PA, USA) with a 6-channel phased-array surface coil and without an endorectal coil. Multiparametric imaging combining axial, sagittal, and coronal T2-weighted, axial diffusion-weighted (b = 50 s mm^{-2}, 800 s mm^{-2}, and 1500 s mm^{-2}), and dynamic contrast-enhanced imaging (10 ml of gadoterate meglumine injected intravenously at 2.5 ml s^{-1}, and axial three-dimensional [3D] volumetric interpolated breath-hold

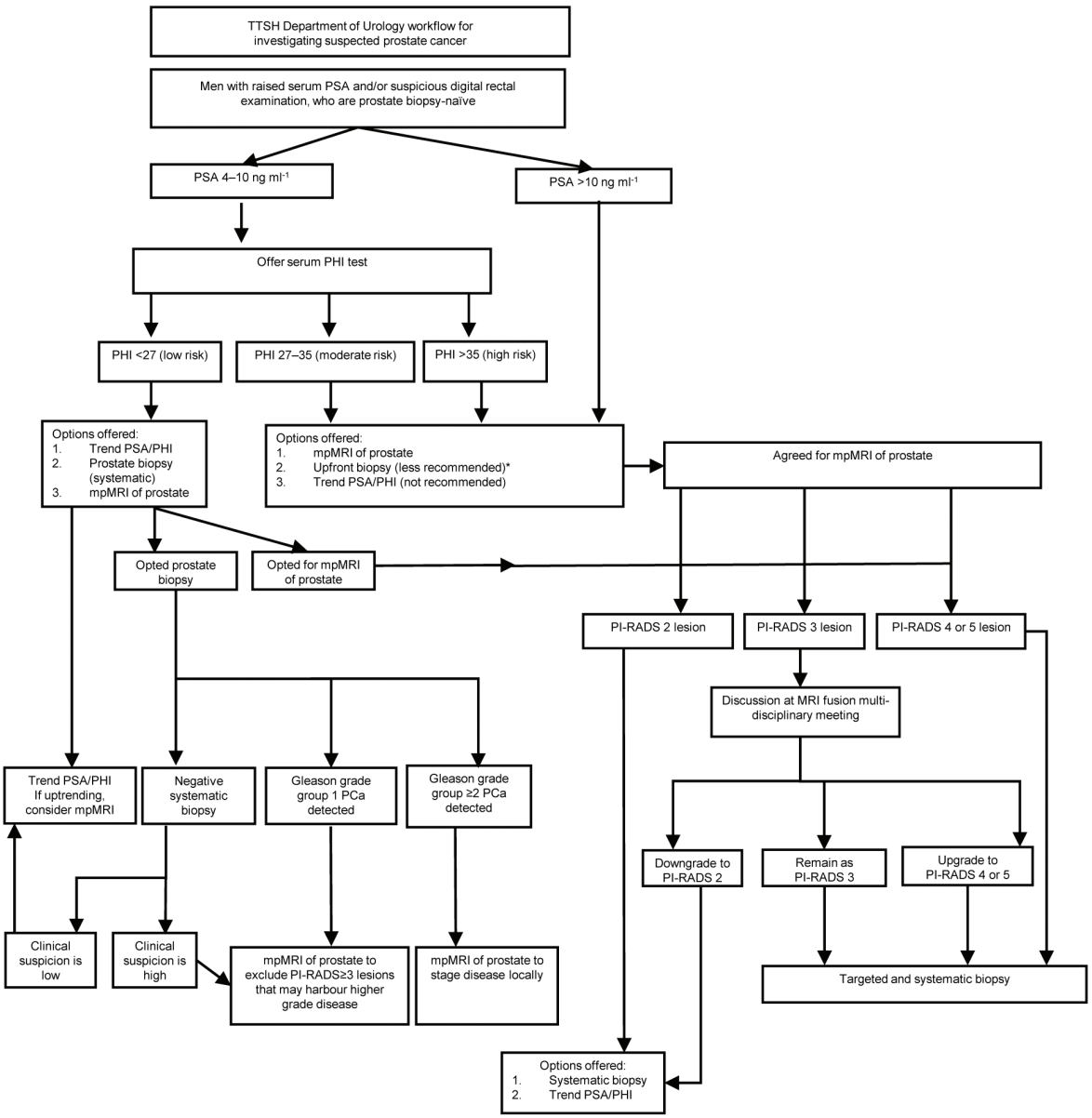

Figure 1: TTSH Department of Urology workflow for investigating suspected prostate cancer. *If PSA markedly elevated (*e.g.*, >50 ng ml^{-1}), risk of prostate cancer is high and upfront systematic biopsy with 6–12 cores is preferred, to minimize delay to the diagnosis of prostate cancer. This is due to our institutional waiting time of 2–3 weeks for mpMRI of prostate. PSA: prostate-specific antigen; PHI: prostate health index; DRE: digital rectal examination; PI-RADS: Prostate Imaging-Reporting and Data System; mpMRI: multi-parametric magnetic resonance imaging; TTSH: Tan Tock Seng Hospital, Singapore.

examination [VIBE] with temporal resolution of 8–10 s) was used to assess for the likelihood of cancer. Two experienced uroradiologists (CHL and CHT) with 15 years' and 10 years' experience in interpreting mpMRI, respectively, reviewed all images. They also segmented the images and marked out the location of the suspicious lesion(s) (DynaCAD; Invivo Corporation, Gainesville, FL, USA).

Biopsy technique

After cleansing the rectum with iodine, we administered a peri-prostatic nerve block using 10 ml of 1% lignocaine local anesthesia. Following which, we performed targeted biopsies using the UroNav MRI-TRUS fusion system (Invivo, Gainesville, FL, USA). Systematic biopsy was then performed by the same clinician who is not blinded to the location of the suspicious lesion(s). Our systematic template uses the double-sextant 12-core biopsy which incorporates apical and far-lateral cores in the template distribution (**Figure 2**); this is currently the recommended sequence endorsed in a recent American Urological Association white paper.[10,11] Generally, if the clinician deemed that the targeted biopsy cores have sufficiently sampled the target lesion, he/she will avoid the lesion during the systematic biopsy in that same region. This has been previously described in detail.[12]

Pathological analysis

Detection ratio was defined by the ratio of the detection rates obtained by MRI-targeted biopsy alone and by systematic biopsy alone. The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique.

When ascertaining sensitivities, specificities, positive and negative predictive values of targeted *vs* systematic biopsies, we defined the true rate of disease detection (any prostate cancer or csPCa) as the combined result of both systematic and targeted biopsies.

Statistical analyses

To determine the factors associated with detection of csPCa, we performed multivariable logistic regression analysis, evaluating factors including PSA density, PHI, PI-RADS score of index lesion, lesion location, and lesion volume-to-prostate volume ratio (defined as the ratio of the index lesion volume-to-prostate volume as measured on mpMRI). All statistical analyses were performed on STATA/SE version 14 (StataCorp, College Station, TX, USA), and two-sided statistical significance was defined as $P < 0.05$.

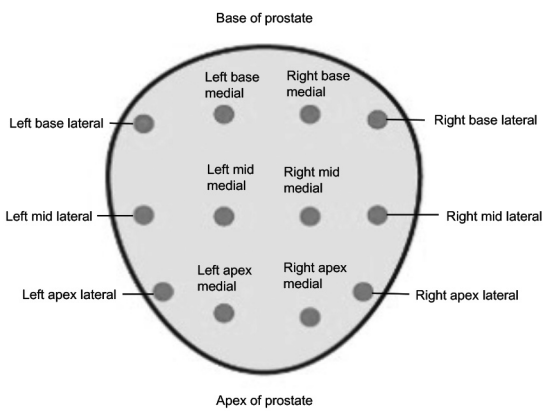

Figure 2: Template for double-sextant 12-core systematic prostate biopsy via transrectal ultrasound guidance.

RESULTS

A total of 545 patients underwent MRI fusion-targeted biopsy between May 2016 to May 2020, of which 222 (40.7%) were biopsy-naïve, 247 (45.3%) had a previous negative prostate biopsy, and 76 (13.9%) were patients with known prostate cancer undergoing active surveillance (**Table 1**). Median age was 69 (interquartile range [IQR]: 65–74) years. Median PSA was 8.98 (IQR: 6.17–13.42) ng ml^{-1}, and median PHI was 34 (IQR: 26–44). A minority of patients (n=74, 13.6%) had suspicious disease (at least cT2) on digital rectal examination.

In terms of the index lesion found on mpMRI prostate, patients who were biopsy-naïve tended to have a higher proportion (62.4%) of high-risk lesions (PI-RADS 4 and 5) compared to patients who had previous negative prostate biopsies (28.6%) and those on active surveillance (31.6%; both $P < 0.001$).

Prostate cancer detection was higher in patients who were biopsy-naïve (63.5%) and undergoing active surveillance (68.4%), compared to those who had previous negative biopsies (35.2%; both $P < 0.001$). Similarly, the rates of csPCa were the highest in the biopsy-naïve group (53.6%), followed by those on active surveillance (42.1%), compared to those with previous negative biopsies (25.5%; $P < 0.001$).

Biopsy-naïve group

PCa and csPCa detection rates were 63.5% (n=141) and 53.6% (n=119), respectively. More csPCa was found in those with higher PI-RADS score (86.8% [PI-RADS 5], 63.0% [PI-RADS 4] and 26.5% [PI-RADS 3]). There were 18 (8.1%) csPCa found on targeted biopsy but not on systematic biopsy. Conversely, there were 23 (10.4%) csPCa found on systematic biopsy and not on targeted biopsy, suggesting an added value of 10.4% (23/222) for systematic biopsy (**Table 2**).

Active surveillance group

A total of 76 patients were identified with a median age of 70.5 (IQR: 67–75) years, median PSA of 7.29 (IQR: 5.03–10.39) ng ml^{-1}, and median PHI of 34 (IQR: 26–44). Among these 76 patients, 12 did not undergo systematic biopsies as they already had two previous systematic biopsies; hence, only targeted biopsies were performed. Among the remaining 64 patients, 40 (62.5%) had any prostate cancer detected on systematic biopsies. Targeted biopsies upgraded 11 (17.2%) patients who did not have csPCa with systematic confirmatory biopsy alone. Conversely, systematic biopsies detected 8 (12.5%) csPCa where targeted biopsies were negative.

Diagnostic performance of systematic vs targeted biopsies

The sensitivities, specificities, and positive and negative predictive values of systematic biopsies compared to targeted biopsies in the detection of any prostate cancer and csPCa are presented in **Table 3**. The negative predictive value of targeted biopsies for detecting csPCa was 89.9% as compared to 85.9% for systematic biopsies.

Added value of systematic and targeted biopsies

The absolute added value of a given biopsy technique was evaluated. We found that MRI-targeted biopsies provided an incremental 8.1% detection of csPCa among biopsy-naïve patients and an additional 7.3% among the previous negative systematic biopsy group (**Table 2**). On the other hand, systematic biopsies provided an incremental 10.4% detection of csPCa among biopsy-naïve patients *vs* an incremental 2.4% among those who had prior negative biopsies. In the overall cohort of 545 men, there were 52 (9.5%) cases of cancers and 37 (6.8%) cases of csPCa detected on systematic biopsies alone where the targeted biopsies were negative.

Table 1: Characteristics of patients who had undergone MRI fusion biopsy of prostate.

Characteristic	*No previous biopsy (biopsy naïve)*[a]	*Previous biopsy*	*Active Surveillance (known prostate cancer)*	*Overall*	*P*
Patient, *n* (%)	222 (40.7)	247 (45.3)	76 (13.9)	545 (100.0)	
Age (year)					
Mean (s.d.)	68.7 (8.0)	69.0 (6.9)	70.4 (6.9)	69.1 (6.9)	
Median (IQR)	68.5 (64-74)	69 (65-74)	70.5 (67-75)	69 (65-74)	
PSA (ng ml^{-1}), median (IQR)	8.53 (6-13.2)	9.91 (6.98-14.86)	7.29 (5.03-10.39)	8.98 (6.17-13.42)	
PHI, median (IQR)	37 (27-49)	33 (26-42)	34.5 (20-45)	34 (26-44)	
Suspicious DRE (at least cT2), *n* (%)	41 (18.5)	26 (10.5)	7 (9.2)	74 (13.6)	0.021
Index lesion PI-RADS score, *n* (%)					<0.001
3	83 (37.6)	159 (64.4)	52 (68.4)	294 (54.0)	
4	100 (45.3)	66 (26.7)	19 (25.0)	185 (34.0)	
5	38 (17.1)	22 (1.9)	5 (6.6)	65 (12.0)	
Patients with a 2nd target lesion (*n*)	67	90	22	178	
PI-RADS score of 2nd target lesion, *n* (%)					0.002
2	2 (2.6)	1 (1.0)	0 (0)	3 (1.5)	
3	42 (54.6)	81 (84.4)	18 (81.8)	141 (72.3)	
4	28 (36.4)	13 (13.5)	4 (18.2)	45 (23.1)	
5	5 (6.4)	1 (1.1)	0 (0)	6 (3.1)	
Prostate cancer detected, *n* (%)	141 (63.5)	87 (35.2)	52 (68.4)	280 (51.4)	<0.001
From systematic biopsy cores (yes/no), *n* (%)	120 (54.1)/94 (42.3)	57 (23.1)/136 (55.1)	40 (52.6)/24 (31.6)	217 (39.8)/253 (46.6)	<0.001
From targeted biopsy cores (yes/no), *n* (%)	122 (55.0)/100 (45.0)	72 (29.2)/175 (70.8)	35 (46.1)/ 41 (53.9)	229 (42.0)/316 (58.0)	<0.001
Clinically significant prostate cancer detected (Gleason ≥7), *n* (%)	119 (53.6)	63 (25.5)	32 (42.1)	214 (39.3)	<0.001
From systematic biopsy cores (yes/no), *n* (%)	96 (43.2)/118 (53.2)	31 (12.6)/162 (65.6)	16 (21.1)/ 48 (63.2)	143 (26.2) /328 (60.2)	<0.001
From targeted biopsy cores (yes/no), *n* (%)	98 (44.1) /124 (55.9)	57 (23.1)/ 190 (76.9)	24 (31.6) /52 (68.4)	179 (32.8)/ 366 (67.2)	<0.001

[a]One biopsy-naïve patient did not have a PI-RADS score available (outside MRI scan). PSA: prostate-specific antigen; PHI: prostate health index; s.d.: standard deviation; IQR: interquartile range; DRE: digital rectal examination; PI-RADS: Prostate Imaging-Reporting and Data System.

Detecting csPCa

In a mixed population (of biopsy-naïve and prior-negative biopsy men), the detection ratio of csPCa was 1.22, meaning that the MRI pathway increased the grade 2 or higher prostate cancer detection rate by 22.0% over systematic biopsy.

In the overall cohort of patients, on univariable logistic regression, we found that age, suspicious digital rectal examination, PSA density, PHI, PI-RADS score, target lesion volume, and lesion volume-to-prostate volume ratio were significant predictors for detecting csPCa on targeted biopsy (**Table 4**). Lesion location (transition *vs* peripheral zone *vs* both) was not significantly associated with csPCa detection. On multivariable logistic regression, we found age (OR = 1.03, 95% CI: 1.00–1.06, $P = 0.03$), PSA density ≥0.15 ng ml^{-2} (OR = 3.24, 95% CI: 2.01–5.23, $P < 0.001$), PHI ≥35 (OR = 2.43, 95% CI: 1.29–4.57, $P = 0.006$), higher PI-RADS score (compared to PI-RADS 3; OR = 4.59, 95% CI: 2.90–7.27 for PI-RADS 4; and OR = 9.91, 95% CI: 4.81–20.43 for PI-RADS 5; both $P < 0.001$) and target lesion volume-to-prostate volume ratio ≥0.10 (*vs* <0.10; OR = 5.26, 95% CI: 1.42–19.39, $P = 0.013$) were significantly associated with csPCa detection on targeted biopsy (**Table 4**).

DISCUSSION

To the best of our knowledge, this is the largest series of MRI fusion-targeted prostate biopsies in south-east Asia. A key finding was the substantial incremental value of systematic biopsies (10.4%), suggesting that this should not be omitted, particularly in biopsy-naïve men. This is consistent with currently available evidence, ranging from 4.3% to 5.2% from the 3 highlighted studies in **Table 2**. Drost *et al*.[5] carried out the Cochrane pooled analysis and found that for every 100 biopsy-naïve men with a positive MRI, MRI fusion-targeted biopsy detected approximately 39 men with csPCa (39.2%, 17 studies, 2955 men), and systematic biopsy detected five additional cases. There is substantial variation in the biopsy techniques utilized by each study and center represented in the Cochrane meta-analysis[5] and the MRI-FIRST trial, ranging from cognitive targeting with MRI/TRUS to even cognitive targeting with contrast-enhanced ultrasound. The 4M trial utilized in-bore MRI-guided biopsy followed by a systematic 12-core TRUS-guided biopsy by a urologist on the same day. As such, it is not unexpected to have some variation in the incremental value of systematic biopsies across studies, including ours. As to why our study detected a relatively high (10.4%) incremental value of systematic biopsy, we believe this is because in the clinical setting, there is a tendency for the proceduralist to attempt to maximize yield, by avoiding overlap with positions covered by targeted biopsy. For example, if the proceduralist targets a PI-RADS 4 lesion (volume: 0.28 ml) at the right apex in a prostate of 50 ml with 4 cores, he/she will then aim for other positions within the right apex during the systematic biopsy (typically 2 cores). The same (Uronav®) software is applied to confirm the regions for systematic biopsy, based on the shape and volume of the gland, to maintain consistency. In a prospective series of 2103 men who underwent MRI targeted and systematic biopsies at the National Cancer Institute in the USA, where the same UroNav system was first invented and utilized, the added value of systematic biopsy was 5.8%; however, this included a mix population of both biopsy-naïve and those with prior biopsies.[14]

The added benefit of detecting csPCa from systematic biopsy cores should be weighed against the potential for added morbidity. Studies have found lower complications with targeted only biopsies and omitting systematic biopsies.[15,16] A prospective survey of 262 men who underwent either MRI-fusion targeted biopsies (median:

Table 2: Absolute added values of targeted and systematic biopsies for International Society of Urological Pathology grade ≥2 cancer detection among patients who were biopsy naïve or had prior negative biopsy

Biopsy status	*Cochrane meta-analysis, % (95% CI)*	*MRI-FIRST trial, % (95% CI)*	*4M trial (5), %*	*TTSH data, n (%)*
Biopsy naïve (*n*=222 for TTSH data)				
Added value[a] of MRI targeted biopsy	6.3 (4.8–8.2)	7.6 (4.6–11.6)	7.0	18 (8.1)
Added value[a] of systematic biopsy	4.3 (2.6–6.9)	5.2 (2.8–8.7)	5.0	23 (10.4)
Overall prevalance	27.7 (23.7–32.6)	37.5 (31.4–43.8)	30.0	119 (53.6)
Prior negative biopsy (*n*=247 for TTSH data)				
Added value[a] of MRI-targeted biopsy	9.6 (7.7–11.8)	-	-	18 (7.3)
Added value[a] of systematic biopsy	2.3 (1.2–4.5)	-	-	6 (2.4)
Overall prevalence	22.8 (20.0–26.2)	-	-	63 (25.5)

[a]The absolute added value of a given biopsy technique is defined by the percentage of patients of the entire cohort diagnosed only by this biopsy technique alone. MRI: magnetic resonance imaging; 4M trial: Met Prostaat MRI Meer Mans; TTSH: Tan Tock Seng Hospital, Singapore; ISUP: International Society of Urological Pathology

Table 3: Accuracy of systematic and targeted prostate biopsies in detecting clinically significant *vs* any prostate cancer

Accuracy	*Clinically significant prostate cancer*		*All prostate cancer*	
	Systematic biopsy, % (95%CI)	*Targeted biopsy, % (95%CI)*	*Systematic biopsy, % (95%CI)*	*Targeted biopsy, % (95%CI)*
Sensitivity	75.5 (68.7–81.5)	82.7 (77.0–87.5)	87.9 (83.1–91.7)	81.4 (76.4–85.8)
Specificity	99.6 (98.0–100.0)	99.4 (97.8–99.9)	100.0 (98.4–100.0)	100.0 (98.6–100.0)
PPV	99.3 (96.2–100.0)	98.9 (96.0–99.9)	100.0 (98.3–100.0)	100.0 (98.4–100.0)
NPV	85.9 (81.7–89.5)	89.9 (86.3–92.8)	88.2 (83.6–91.9)	83.5 (79–87.5)

CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value

Table 4: Predictors of detecting clinically significant prostate cancer on targeted biopsy

Variable	*Univariable analyses*			*Multivariable analyses*		
	OR	*95% CI*	*P*	*OR*	*95% CI*	*P*
Age (year)	1.04	1.02–1.07	0.001	1.03	1.00–1.06	0.03
Suspicious DRE	2.63	1.60–4.33	<0.001	1.11	0.59–2.08	0.31
PSA density (ng ml^{-2})						
<0.10	Reference			-	-	-
≥0.10	6.43	3.16–13.09	<0.001	-	-	-
PSA density (ng ml^{-2})						
<0.15	Reference			Reference		
≥0.15	4.47	2.91–6.87	<0.001	3.24	2.01–5.23	<0.001
Prostate health index						
<27	Reference			-	-	-
≥27	6.02	2.37–15.34	<0.001	-	-	-
Prostate health index						
<35	Reference			Reference		
≥35	3.83	2.18–6.72	<0.001	2.43	1.29–4.57	0.006
PI-RADS score of index lesion						
3	Reference			Reference		
4	4.96	3.22–7.66	<0.001	4.59	2.90–7.27	<0.001
5	19.46	10.04–37.70	<0.001	9.91	4.81–20.43	<0.001
Target lesion volume (ml)	1.33	1.16–1.53	<0.001	-	-	-
Lesion volume-to-prostate volume ratio						
<0.10	Reference			Reference		
≥0.10	14.01	4.78–41.06	<0.001	5.26	1.42–19.39	0.013
Lesion location						
Transitional zone	Reference					
Peripheral zone	1.04	0.72–1.50	0.823	-	-	-
Both	1.48	0.55–4.04	0.439	-	-	-

DRE: digital rectal examination; PSA: prostate-specific antigen; PI-RADS: Prostate Imaging-Reporting and Data System; CI: confidence interval

3 cores) or systematic biopsies (median: 12 cores) in Finland showed that at 30 days, a higher proportion in the systematic biopsy group had experienced pain (34% *vs* 20%, $P = 0.04$) and hematuria (69% *vs* 44%, $P < 0.001$) than in the fusion biopsy group.[16]

In a Cochrane pooled analysis of 25 studies by Drost *et al*.,[5] comparing systematic biopsy (median number of 8–15 cores) to MRI-targeted biopsies (median number of 2–7 cores), the detection ratio for ISUP grade ≥2 was 1.12, in favor of MRI-targeted biopsies. This ratio was found to be lower in biopsy-naïve patients (1.09), compared to that in patients with prior negative systematic biopsies (1.44).[5] This was in concordance to what our study found, with a detection ratio of 1.22 overall, and 1.02 in biopsy naïve patients *vs* 1.84 in prior negative biopsy patients. Our relatively low detection ratio among biopsy naïve patients was similar to that found in the MRI-FIRST trial (32.3% *vs* 29.9%, $P = 0.38$; detection ratio: 1.08).[3]

In a recent Cochrane meta-analysis which compared mpMRI to template biopsies (>20 cores) in biopsy-naïve and repeat-biopsy settings, mpMRI had a pooled sensitivity of 0.91 (95% CI: 0.83–0.95) and a pooled specificity of 0.37 (95% CI: 0.29–0.46) for ISUP grade >2.[5] Although our study did not have a reference standard of either a saturation template biopsy or a radical prostatectomy histologic specimen, using the combined detection rate of csPCa, we were able to determine the diagnostic performance characteristics of systematic *vs* targeted biopsies.

It should be noted that systematic biopsies can address the limitations of MRI in detecting csPCa. Some novel work has been done in this space to evaluate the role of gallium-68 prostate-specific membrane antigen positron-emission tomography/computed tomography (^{68}Ga-PSMA PET/CT) to localize prostate cancer foci. Donato *et al*.[17] performed a retrospective analysis of 144 patients who underwent mpMRI, prostate biopsy and ^{68}Ga-PSMA PET/CT over a 3-year period, and found that while index lesion/foci detection was similar between ^{68}Ga-PSMA PET/CT and mpMRI (sensitivity: 83.1% *vs* 90.1%; $P = 0.267$), lesions missed by mpMRI were larger (1.66 cm^3 *vs* 0.72 cm^3; $P = 0.034$). The incremental detection yield favored ^{68}Ga-PSMA PET/CT over mpMRI for index (13.5% *vs* 4.3%) and total (18.2% *vs* 5.4%) lesions. Using whole mount radical prostatectomy specimens for tumor concordance, both modalities were found to have missed 2.1% and 12.3% of index and total lesions, respectively. Another smaller study of 56 consecutive patients with ISUP grade 2–3 PCa after radical prostatectomy, who underwent both mpMRI and PSMA-PET/CT preoperatively, found that PSMA-PET demonstrated greater diagnostic accuracy with an area under curve of 0.91 (*vs* 0.79 for mpMRI) and a negative predictive value of 85% (*vs* 75% for mpMRI).[18] As such, it is not surprising that the role of ^{68}Ga-PSMA PET/CT to localize prostate cancer will be further evaluated in a prospective fashion with the PRIMARY trial in Australia, a multi-center prospective, cross-sectional study of the additive diagnostic value of ^{68}Ga-PSMA PET/CT to mpMRI in the diagnostic setting for men being investigated for prostate cancer.[19]

Worth mentioning is that the added value of MRI targeted biopsy among biopsy naive men in our study is 8.1%, similar to the 6.3%–7.5% in the literature (**Table 2**). At our institution, all PI-RADS 3 lesions are discussed at a monthly multi-disciplinary meeting, where independent reviews by dedicated uroradiologists are carried out. These lesions may be upgraded to PI-RADS 4 or 5, be downgraded to PI-RADS 2, or remain as PI-RADS 3. We believe that such a review process eliminates benign lesions from unnecessary targeted biopsy and consequently leads to higher detection of csPCa than reported elsewhere.[20]

Finally, our multivariable analysis has identified some significant factors to predict detection of csPCa on targeted biopsy. We hypothesized that larger lesions within a smaller prostate (higher lesion volume-to-prostate volume ratio) tend to harbor more significant disease compared to smaller lesions (lower lesion volume-to-prostate volume ratio). Interestingly, univariable analysis confirmed that the larger the target lesion, the higher the odds of detecting csPCa. Adjusting for other confounders such as PSA density, PHI and PI-RADS score of the index lesion, higher lesion volume-to-prostate volume ratio remained a significant predictor (OR = 5.26, $P = 0.013$). Serum PSA adjuncts such as PHI, commonly used at our institution for men with PSA between 4 ng ml^{-1} and 10 ng ml^{-1}, can help better risk-stratify our patients, particularly those determined to be PI-RADS 3, and also help in counseling patients either for, or against, adding on targeted biopsy.

Despite strengths, our study is not devoid of limitations. First, we do not have whole-mount histology capabilities and as such are not able to correlate the MRI targeted and systematic biopsies to whole-mount radical prostatectomy specimens.[21] Efforts are underway to create an additional billing code to aid research and clinical correlation between the MRI lesion and eventual radical prostatectomy specimen. Second, we did not subject our patients to a separate template saturation biopsy in an attempt to get to a more accurate reference standard of prostate cancer detection. Third, our systematic biopsy only utilized the double-sextant template, which yields only 12 cores via the transrectal approach. This achieves fewer number of systematic cores which can range from 18 to 24 cores using the transperineal approach.[22] The 2021 European Association of Urology Guidelines do recommend 10–12 core biopsies for transrectal biopsy and stated that >12 cores have not been shown to be significantly more conclusive.[23–25]

CONCLUSIONS

In this large series of men who underwent MRI fusion-targeted prostate biopsies, we found that systematic biopsies should not be omitted given its incremental value to targeted biopsies alone. The factors such as PSA density ≥0.15 ng ml^{-2}, PHI ≥35, higher PI-RADS score and target lesion volume-to-prostate volume ratio ≥0.10 can help identify men at higher risk of csPCa.

AUTHOR CONTRIBUTIONS

JJL carried out the data collection, performed the statistical analysis, and drafted the manuscript. SHK, WL, MWLC, RS II, SKH, and YY carried out data collection, and participated in the study design and coordination of weekly biopsies and meetings. CHL and CHT read all the mpMRI prostate images in the setting of a multidisciplinary meeting and participated in its design and coordination. TWT conceived of the study, supervised the entire project, and critically revised the manuscript. All authors interpreted the data, critically revised the manuscript, read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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