Transrectal ultrasound-guided biopsy for prostate cancer detection: Systematic and/or magnetic-resonance imaging-targeted

Franck Bladou, MD[1]; Cora Fogaing, MD[1]; Mark Levental, MD[2]; Samuel Aronson, MD[1]; Mona Alameldin, MD[3]; Maurice Anidjar, MD[1]

[1]Department of Urology; [2]Department of Radiology; [3]Department of Pathology; Jewish General Hospital, McGill University, Montreal, QC, Canada

Cite as: *Can Urol Assoc J* 2017;11(9):E330-7. http://dx.doi.org/10.5489/cuaj.4308
Published online September 12, 2017

Abstract

Introduction: Magnetic resonance imaging (MRI) is being more widely used in the detection of prostate cancer (PCa), particularly after an initial negative biopsy. In this study, we compared 12-core systematic biopsy (SYS), MRI-targeted biopsy (TAR), and the association of systematic and MRI-targeted (SYS+TAR) prostate biopsy in patients with previous biopsy and those who were biopsy-naive to evaluate the differences in terms of cancer detection and clinically significant cancer detection between the three modalities.
Methods: Overall, 203 consecutive patients with suspicion of PCa were analyzed; 48.2% were biopsy-naive and 51.7% had at least one previous negative prostate biopsy. The median age was 66 years, median prostate-specific antigen (PSA) level was 7.9 ng/mL and median prostate volume was 46 mL. 38.9% had SYS, 19.2% TAR only, and 41.8% had SYS+TAR biopsy.
Results: Overall, the PCa detection (PCaDR) was 63%. The SYS+TAR biopsy detected significantly more cancer than SYS and TAR only biopsies (72.9% vs. 56.9% and 53.8% respectively; p=0.03). Detection rate of clinically significant cancer (csPCaDR) was 50.7% overall; 65.8% in the SYS+TAR biopsy vs. 39.2% in the SYS and 48.7% in the TAR groups (p=0.002). In the biopsy-naive group, PCaDR and csPCaDR were significantly higher in the SYS+TAR group than in the SYS and TAR groups (p=0.01). In the repeat biopsy group, PCaDR and csPCaDR were equivalent in the TAR and SYS+TAR groups and higher than in the SYS group (p=0.001).
Conclusions: TAR biopsy, when added to SYS biopsy, was associated with a higher detection rate of csPCa in biopsy-naive patients when compared to TAR and SYS only biopsies. In patients after previous negative biopsy, detection rates of csPCa were equivalent for SYS+TAR and TAR only biopsies, but higher than SYS.

Introduction

Prostate cancer (PCa) is the most common cancer diagnosed in men in Canada and the second most common cause of cancer death.[1] As prostate cancer is a histopathological diagnosis, men with rising prostate-specific antigen (PSA) or abnormal digital rectal examination (DRE) are usually referred for a prostate biopsy. Traditional ultrasound-guided prostate biopsy has been shown to have limited sensitivity for detecting PCa.[2,3] It consists of a systematic 12-core biopsy distributed to the peripheral prostate gland from base to apex on each side. Tissue harvesting is done without targeting and may miss aggressive disease or randomly detect insignificant disease, i.e., low-volume of Gleason score (GS) 6 cancer. The accuracy of different biopsy strategies for detecting clinically significant PCa has been studied, particularly in one study using computer simulation.[4] The results showed that systematic transrectal ultrasound biopsy performed poorly and the optimal performance was obtained using a 5 mm sampling frame transperineal template prostate mapping with increased number of biopsy cores.

Several options have been studied in order to improve the accuracy of systematic prostate biopsy for the diagnosis of cancer, including increasing the number of biopsies as in the saturation biopsy scheme,[5] using predictor markers,[6] and using pre-biopsy imaging such as multiparametric magnetic resonance imaging (mpMRI) to direct the needle to the regions of interest.[7-9] Results from the PROMIS study favour the use of upfront prostate mpMRI to triage biopsy-naive men when compared to systematic 10–12-core biopsy.[10] Other studies have shown the superiority of MRI-targeted biopsy compared to systematic 12-core biopsy, particularly in patients with previous negative biopsy.[11-14] Reviews and meta-analyses have demonstrated sensitivity and specificity between 70–90% for the detection of clinically significant prostate cancer (csPCa).[15-18] Thus, MRI is increasingly used in the PCa diagnostic pathway and may influence the decision of whether or not to perform a biopsy. The type of biopsy, performed either by transrectal or transperineal route, may be different using a mpMRI. The targeting could be performed by visual estimation (cognitive fusion) or using a MRI-ultrasound (US) image fusion software system.[19]

The objective of the present study was to compare the PCa detection rate using targeted prostate biopsy (TAR), performed with cognitive and automated MRI-US image fusion, and 12-core systematic biopsy (SYS), in a population of men with increased PSA and/or abnormal DRE, with or without history of negative prostate biopsy.

Methods

Study design and population

From January 2014 to October 2016, 224 consecutive men referred to one urologist in our institution for prostate biopsy were analyzed. Of the 224 men, 21 patients were excluded from the analysis because of a PSA greater than 30 ng/mL and/or a prostate volume greater than 120 mL. As a regional reference centre for prostate biopsy, our centre receives referrals from both community and academic urologists, and men are referred either for upfront systematic biopsy or with an initial MRI ordered by the referring physician, performed either in our institution or another institution where mpMRI is available. Clinical data, MRI parameters, and biopsy results were recorded in an institutional review board-approved database.

mpMRI

When performed in our institution, mpMRI was on a 1.5 then a 3 Tesla whole body system and a pelvic phased array coil. It included multiplanar turbo-spin echo T2-weighted images, axial single shot echo-planar imaging diffusion-weighted imaging with b-values of 50 and 1400 seconds per mm^2, and dynamic contrast-enhanced imaging MRI after intravenous administration of gadolinium chelate. A detailed description of MRI acquisition and the post-processing of images performed in our institution has been reported.[20] Patients were also referred to our centre with mpMRI done in other institutions and were reviewed by both the urologist and the radiologist with five years of experience in prostate MRI reading of greater than 500 MRI-prostate at the start of this study. The level of cancer suspicion for MRI-detected lesions was graded on the overall impression based on analysis of T2w images, diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps, and gadolinium-enhanced dynamic images using a five-point Likert scale: score 1–2 low probability; 3 equivocal; 4 high probability; and 5 very high probability as previously reported.[21] When the mpMRI report done outside our institution stated a range Likert rating, such as Likert 1–2, 2–3, 3–4, or 4–5, the highest number was chosen, explaining why some suspicious areas indicated as Likert 2 were biopsied.

Systematic and MRI-US fusion-targeted biopsy

All biopsies were performed on patients in left lateral decubitus position and under prophylactic antibiotics (quinolone). Local 1% xylocaine gel was introduced in the anus before insertion of the US probe and 10 mL of 1% xylocaine was injected at the level of both prostate base and apex on each side of the gland. Biopsies were guided using a B&K FlexDuo ultrasound machine (BK medical, QC, Canada) in the first 123 patients and with a Samsung H60 V2 (Apexium Medical Group, QC, Canada) in the following 80 patients, with an end-fire probe, re-usable biopsy gun, and 18-gauge needles.

From January 2014 to February 2016, TAR was performed with a cognitive approach in 49 patients; mpMRI studies were reviewed before biopsy to identify suspicious foci in the prostate, as described in the radiology report form. The mpMRI potential target(s) were drawn on a sector map according to the international scoring system for prostate sectors[22] and used during the procedure as an optical guide for the needle direction. From March to October 2016, all TAR were been performed using the Urostation™ (Koelis, Grenoble, France) in 75 patients. Briefly, prostate and lesion boundaries were identified by the urologist and the radiologist on T2-weighted images and transferred to the Urostation™ for guidance during the biopsy procedure. Computer assisted co-registration of segmented MRI and US images of the prostate was performed by automated elastic deformation. In the SYS+TAR group, transrectal biopsies were obtained, beginning with 12-core systematic biopsy with the potential targets blinded and followed by a median of three targeted biopsies of each suspicious lesion identified on mpMRI. In the TAR group, the median number of biopsy was six per target.

For each patient, all SYS and TAR were performed by the same urologist (FB) with expertise in prostate biopsy. Systematic 12-core biopsies were taken on sectors 1p-2p-3p-4p-5p and 6p on the right lobe and 7p-8p-9p-10p-11p and 12p on the left lobe according to the European recommendations of prostate segmentation.[19] Additional MRI-targeted biopsies were recorded using the same scheme. All biopsy cores were sent separately and analyzed by two specialized genitourinary pathologists at the same institution, using the same scheme code to differentiate the biopsies.

Data analysis and statistics

Results have been reported according to the START recommendations.[23] Biopsy results were compared using the highest GS obtained by each technique. Clinically significant cancer was assessed by the presence of any Gleason pattern 4 or greater in the biopsy (GS 7–10) and/or lesion volume more than 0.5 ml.[24] Other comparative data points included the

number of biopsy cores taken and the ones demonstrating cancer. All analyses were done in XSTAT 2016.06.36439. Categorical variable comparisons were performed with the chi-squared test and continuous variables were evaluated with the Student t-test. Comparison of cancer detection rates between techniques was assessed by the Wilcoxon, Mann-Whitney test. A $p<0.05$ was considered to indicate statistical significance.

Results

Patient demographics

Of the 203 patients analyzed, 79 (38.9%) had systematic 12-core transrectal ultrasound-guided prostate biopsy (SYS) with no mpMRI, 39 (19.2%) had MRI-targeted transrectal ultrasound-guided prostate biopsy only (TAR), either cognitive (n=13) or using a MRI/US image fusion software (Urostation™) (n=26), and 85 (41.8%) had a combination of systematic 12-core followed by MRI-targeted transrectal ultrasound-guided prostate biopsy (SYS+TAR), either cognitive (n=51) or with Urostation™ (n=34).

In this cohort of 203 consecutive men, 98 were biopsy-naive (48.2%) and 105 had at least one previous negative prostate biopsy (51.7%); 80 had one previous biopsy (76.1%), 14 had two previous prostate biopsies (13.3%), and 11 more than two previous prostate biopsies (10.4%).

Table 1 lists patient demographics. There was no difference between the biopsy-naive and repeat biopsy groups in terms of age, initial PSA, and prostate volume, but there was a higher PSA density in the repeat-biopsy group (p=0.04).

Overall cancer detection and clinically significant cancer detection

Table 2 lists the overall PCa and csPCa detection rate (DR) for each biopsy technique. The PCaDR was 63% (128/203). In the biopsy-naive group, the PCaDR was 69.3% (68/98) and in the repeat-biopsy group, the PCaDR was 57.1% (60/105).

While in the SYS group, detection of cancers was slightly higher than in the TAR group (56.9% vs. 53.8%, respectively; p=0.75), more csPCa was detected in the TAR group than in the SYS group (48.7% vs. 39.2%, respectively; p=0.47). In the SYS+TAR group, detection of PCa and csPCa were significantly higher than in the SYS and TAR groups (72.9% vs. 56.9% and 53.8%, respectively for PCaDR [p=0.03] and 65.8% vs. 39.2% [p=0.002] and 48.7% [p=0.07], respectively for csPCaDR).

In the SYS+TAR group, there was a 26.6% increase in csPCa detection compared to the SYS group and a 17.1% increase in csPCa detection compared to the TAR group.

In the biopsy-naive group, csPCaDR was significantly higher in the SYS+TAR group than in the SYS and TAR only groups (72.0% vs. 45.8% [p=0.01] and 0%, respectively). In the repeat-biopsy group, csPCaDR was equivalent between the SYS+TAR and TAR groups (59.5% and 59.3%, respectively) and significantly higher than in the SYS group (29.0%) (p=0.001).

The total number of biopsy cores performed in 203 patients was 2470, 947 in the SYS group, 251 in the TAR group, and 1272 in the SYS+TAR group. Prostate cancer was detected in 18.7%, 35.4%, and 30.3% of the total cores in the SYS, TAR, and SYS+TAR groups, respectively ($p<0.001$ for SYS+TAR and TAR vs. SYS). By dividing the type of biopsy cores, there was a total of 1959 systematic cores with a positive rate of 22.5% (441/1959) and a total of 511 targeted cores with a positive rate of 41.4% (212/511) ($p<0.0001$).

GS 6 PCa was found in 20.3% (26/128), GS 7 in 51.5% (66/128), and GS 8–10 in 28.1% (36/128) of the patients (Fig. 1). GS 6 PCa was higher in the SYS group than in the TAR and SYS+TAR groups (33.3% vs. 14.2% and 12.9%, respectively) and GS 7 was higher in the SYS+TAR group than in the SYS and TAR groups (66.1% vs. 37.7% and 38.0%, respectively); however, GS 8–10 was higher in the TAR group than in the SYS and SYS+TAR groups (47.6% vs. 28.8% and 20.9%, respectively) (Fig. 1). On a per-core analysis, the rate of GS 6 positive cores was 25.4% for SYS and 16.2% for TAR (p=0.14), but the rate of GS 7 and GS 8–10 were not significantly different between SYS and TAR (51.8% vs. 55.4% and 22.6% vs. 28.3%, respectively).

Table 3 lists the cancer detection rates (CDR) in the SYS+TAR group of men. Of 85 men, 62 (72.9%) were found to have PCa. In this subgroup, a total of 1272 biopsy cores were performed, 1012 systematic and 260 targeted. The rate of positive cores was 30.3% (386/1272) for all the cores and 25.9% (263/1012) and 47.3% (123/260) for the systematic and targeted cores, respectively ($p<0.0001$). GS 6, GS 7,

Table 1. Patient demographics: Overall, biopsy-naive, and repeat-biopsy patients

	All	Biopsy-naive	Repeat-biopsy	p
Number of patients	203	98	105	
Median (range)				
Age, years	66 (46–83)	65 (46–82)	66 (48–83)	0.90
PSA level, ng/mL	7.9 (0.7–30)	7.9 (1–30)	7.9 (0.7–30)	0.33
Prostate volume, mL	46 (9.4–120)	50 (13.6–120)	43 (9.4–120)	0.23
PSA density, (ng/mL)/mL	0.16 (0.03–1.39)	0.15 (0.03–0.95)	0.18 (0.03–1.39)	0.04

PSA: prostate-specific antigen.

Table 2. Cancer detection rates according to the type of biopsy

	SYS	TAR	SYS+TAR	TOTAL	p
Group size, n	79	39	85	203	
Biopsy-naive group, n	48	7	43	98	
Repeat-biopsy group, n	31	32	42	105	
PCa detection rate, n (%)	45 (56.9)	21 (53.8)	62 (72.9)	128 (63.0)	**0.03** SYS+TAR vs. SYS and SYS+TAR vs. TAR
Biopsy-naive group, n (%)	31 (64.5)	2 (28.5)	35(81.3)	68 (69.3)	
Repeat-biopsy group, n (%)	14 (45.1)	19 (59.3)	27(64.2)	60 (57.1)	**0.75** TAR vs. SYS
csPCa detection rate, n (%)	31 (39.2)	19 (48.7)	56 (65.8)	103 (50.7)	**0.002** SYS+TAR vs. SYS **0.07** SYS+TAR vs. TAR
Biopsy-naive group, n (%)	22 (45.8)	0	31 (72.0)	53 (54.0)	**0.47** SYS vs. TAR **0.01** SYS+TAR vs. SYS
Repeat-biopsy group, n (%)	9 (29.0)	19 (59.3)	25 (59.5)	49 (46.6)	**0.001** SYS+TAR vs. SYS and TAR vs. SYS

csPCa: clinically significant prostate cancer; PCa: prostate cancer; SYS: systematic 12-core transrectal ultrasound-guided prostate biopsy; TAR: magnetic resonance imaging (MRI)-targeted transrectal ultrasound guided prostate biopsy; SYS+TAR: systematic 12-core and MRI-targeted transrectal ultrasound-guided prostate biopsy.

and GS 8–10 detection rates were similar in the systematic and the targeted biopsies in this group, 19.6% vs. 16.9%, 62.2% vs. 62.2%, and 18.0% vs. 20.7%, respectively. The systematic biopsies did not detect five of 54 csPCa (9.2%) and the targeted biopsies did not detect 10 (18.5%) of the csPCa (p=0.10). Most of the csPCa missed by targeted biopsies were 3+4 GS (8/10), but two GS 9 were not detected (no cancer in one case and GS 3+4 in another case).

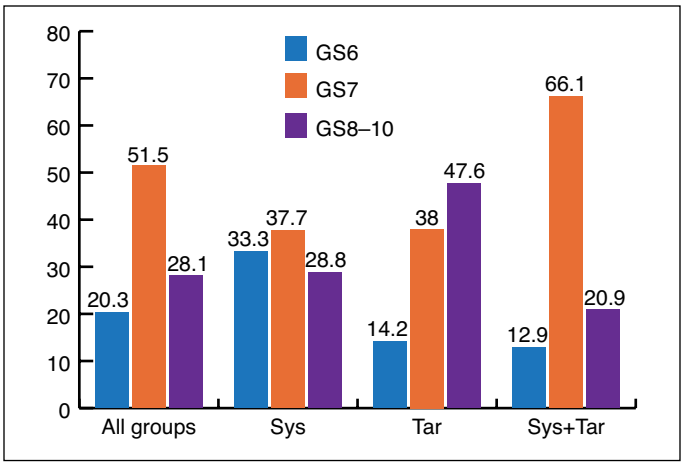

Fig. 1. Distribution of higher Gleason score (GS) in all prostate cancer patients (n=128) diagnosed by systematic 12-core biopsy (SYS), magnetic resonance imaging (MRI)-targeted biopsy only (TAR) and combination of systematic 12-core and MRI-targeted biopsy (SYS+TAR).

MRI suspicion score and PCa detection

One hundred and twenty four men had an initial MRI before the biopsy, 51 from the biopsy-naive group and 73 from the repeat biopsy group. Heterogeneity in the mpMRI quality performed in several institutions made it difficult to perform an accurate classification of MRI targets; however, of the 124 mpMRI analyzed, there were 11 (estimated) Likert 1–2 lesions (8.8%), 18 Likert 3 (14.5%), 52 Likert 4 (41.9%), and 43 Likert 5 (34.6%). In the biopsy-naive group, the distribution of the Likert score lesions were three Likert 1–2, seven Likert 3, 24 Likert 4, and 16 Likert 5. The pathology results from the targeted biopsies performed in the biopsy-naive group are summarized in Fig. 2A, showing a 45.8% and 37.5% rate of negative biopsy in the Likert 4 and 5 lesions, respectively. In the repeat-biopsy group, the distribution of Likert score lesions was eight Likert 1–2, 11 Likert 3, 28 Likert 4, and 27 Likert 5; the results of the targeted biopsies for this group are shown in Fig. 2B. In this group, the GS 8–10 cancer represented 21.4% and 37.0% of the Likert 4 and 5 lesions, respectively. In the biopsy-naive group, anterior lesions were suspected in 4/50 (8%) of the cases and in 14/74 (18.9%) in the repeat-biopsy group (p=0.09).

In the 124 patients with mpMRI done before the biopsy, targeting has been performed with cognitive fusion in 49 patients and using the Urostation™ MRI/US image software fusion in 75 patients. The PCaDR was 61.2% (30/49) in the cognitive-fusion group and 70.6% (53/75) in the software-fusion group (p=0.27). The csPCaDR was 55% (27/49) in the

Table 3. Comparison of pathology results from systematic and MRI-targeted biopsy performed in the same group of patients (group SYS+TAR, n=85)

Systemic 12-core biopsy results	Targeted MRI/ultrasound biopsy results						
	No cancer	Gleason 6	Gleason 3 + 4	Gleason 4 + 3	Gleason 8	Gleason 9	Total
No cancer	**23**	0	0	1	0	0	24
Gleason 6	5	**3**	2	2	0	0	12
Gleason 3 + 4	2	6	**15**	2	0	1	26
Gleason 4 + 3	1	0	4	**6**	1	0	12
Gleason 8	0	0	0	0	**4**	1	5
Gleason 9	1	0	1	0	0	**4**	6
Total	32	9	22	11	5	6	85

SYS+TAR: systematic 12-core and magnetic resonance imaging (MRI)-targeted transrectal ultrasound-guided prostate biopsy.

cognitive-fusion group and in 64.0% (48/75) in the software-fusion group (p=0.32).

Complication rate

Overall complication rate was 6.4% (13/203), including urosepsis in six patients (2.9%, four patients from the SYS group, one patient from the TAR group, and one patient from the SYS+TAR group), urinary retention in three patients (1.4%), hematuria and/or rectal bleeding in three patients (1.4%), and orchitis in one patient (0.5%).

Discussion

In recent years, the use of mpMRI for improving prostate cancer diagnosis prior to biopsy has generated tremendous interest.[25,26]

In our study, three different types of prostate biopsy have been analyzed in a mixed population that comprised men who were biopsy-naive (48.2%) and men who had undergone at least one previous negative biopsy (51.7%). Similarly to others, this study has shown higher CDR by adding TAR compared with a SYS approach and that targeting increases the proportion of men with csPCa. The SYS and TAR biopsy groups show equivalent CDR (56.9% vs. 53.8%), but a higher CDR for csPCa in the TAR group compared to SYS group (48.7% vs. 39.2%; p=0.47) with a significant lower number of cores. Adding SYS+TAR improved both the overall PCaCDR and csPCaCDR (72.9% and 65.8%; p=0.03 and p=0.002, respectively). In the 128 men diagnosed with PCa, there was more GS 6 PCa in the systematic vs. targeted biopsies (25.4 vs. 16.2%) and more csPCa in the targeted vs. systematic biopsies (84.0 vs. 74.5%), but the differences did not reach statistical significance. In the study by Kasivisvanathan et al, a prostate biopsy strategy using only mpMRI-targeted cores resulted in the same detection rate of clinically significant cancer as 20-sector transperineal biopsies.[27] Haffner et al have also shown that a targeted-alone

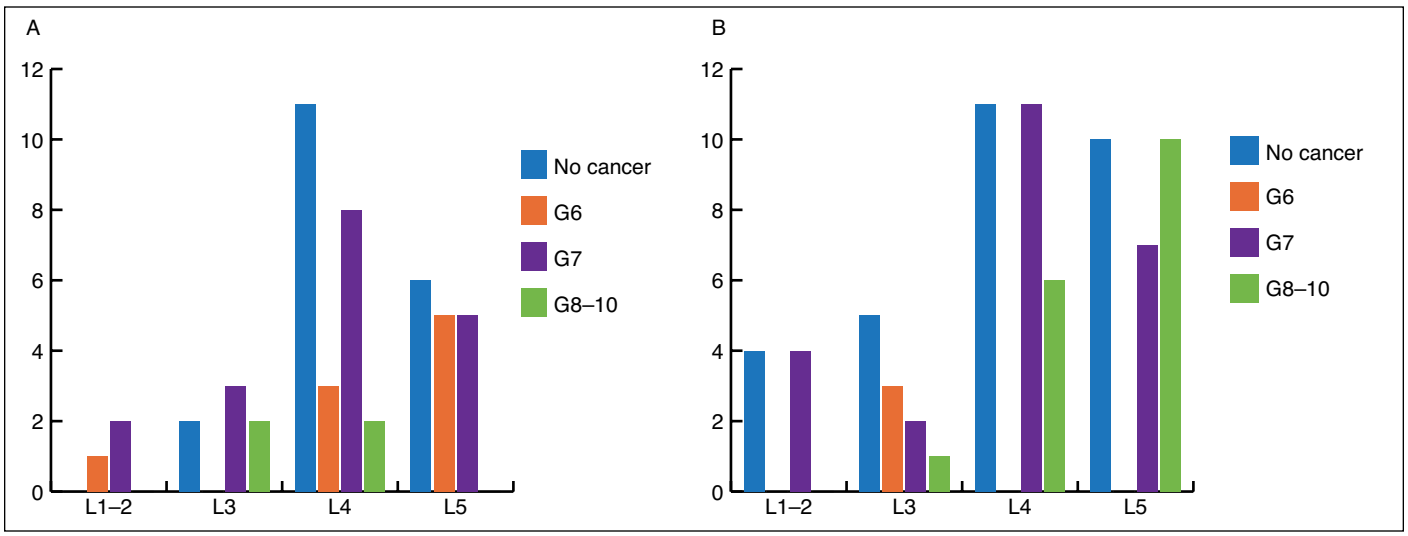

Fig. 2. Repartition of magnetic resonance imaging (MRI) targets by Likert score and pathology results from the targeted biopsies in biopsy-naive (n=50) and repeat biopsy (n=74) group of patients. ***(A)*** In the biopsy-naive group, there were more clinically significant prostate cancers detected in Likert 4 and 5 targets with a high rate of negative biopsy compared to Likert 1–2 and 3 targets; ***(B)*** in the repeat-biopsy group, the rate of Gleason score (GS) 7 and 8–10 was significantly higher in the Likert 4 and 5 targets compared to the Likert 1–2 and 3 groups, but with a high rate of negative biopsy.

approach would detect a similar amount of clinically significant cancer when compared to a 10–12-core systematic transrectal ultrasound (TRUS)-guided biopsy.[28] Sidiqui et al have shown that a targeted-alone approach detects 17% less clinically insignificant cancer compared to systematic TRUS-guided biopsy.[29] In the present study, the GS 6 detection rate was 25.4% in the systematic biopsy vs. 16.2% in the targeted biopsy, a 9% difference (p=0.14).

The detection rates achieved with a targeted-alone biopsy strategy require fewer biopsy cores than systematic TRUS-guided biopsy. In this study, prostate cancer was detected in 24.5% of the total cores, in 20.5% of the 2150 systematic cores, and in 41.7% of the 513 targeted cores (p<0.001). Thus, on a per-core analysis, TAR is more efficient than SYS. In a systematic review by Moore et al, cancer was detected in 30% of all targeted cores in a pooled analysis of 1252 targeted cores compared to 7% of all systematic TRUS-guided biopsy cores in a pooled analysis of 5441 systematic cores.[30]

The 56.9% CDR performed by systematic biopsy in our study is relatively high compared to other recent series from the literature, such as 34% in Borkowetz et al[31] and 44.2% in the meta-analysis from Wu et al,[32] but comparable to others, such as 56.5% in Siddiqui et al[12] or 56.6% in Mozer et al;[14] however, the overall 39.2% CDR for csPCa achieved by systematic biopsy is comparable to most recently published studies, ranging from 26.2–36.8%.[11,12,14,32]

Comparing biopsy-naive men with those after at least one previous negative biopsy, overall CDR and CDR for csPCa were higher in the biopsy-naive group vs. repeat biopsy (69.3 vs. 57.1% and 54 vs. 46.6%, respectively). In the biopsy-naive patient, the use of upfront prostate mpMRI is still controversial and it is not recommended by most scientific societies. In our study, the benefit of adding upfront mpMRI in biopsy-naive patients for a greater CDR of csPCa was in the SYS+TAR group compared to the SYS group, 72.0% vs. 45.8%, respectively (p=0.01). The recent publication of the results from the PROMIS paired validating confirmatory study bring confirmation, as level 1b evidence, that using upfront prostate mpMRI to triage biopsy-naive men could avoid unnecessary biopsy in 27% of the cases while diagnosing 5% fewer clinically insignificant PCa when compared to systematic 10–12-core biopsy.[10] Only randomized trials will confirm the potential benefit for upfront MRI in biopsy-naive patients, such as the PRECISE study that will be soon launched in Canada, to determine if mpMRI can improve our ability over SYS to diagnose csPCa and our ability to avoid detecting clinically insignificant cancer. Meanwhile, we would not recommend the use of prostate MRI in all patients, as the access to and the costs linked to it have not yet been evaluated.

In the repeat-biopsy group, our results showed a greater CDR for csPCa in the TAR group compared to the SYS group (56.2% vs. 25.8%; p=0.001), and comparable to the SYS+TAR group (54.7%) with a significantly lower number of cores. As already described in other studies, anterior lesions, usually not accessible to systematic biopsies, were more frequent in the repeat-biopsy group than in biopsy-naive group, 18.9% vs. 8%, respectively (p=0.09). Using mpMRI in this group of patients is beneficial, as it allows a sampling of unusual tumour locations, i.e., central and transitional zones of the prostate, that are typically not reached by SYS.[7] The National Institute for Health and Care Excellent (NICE) and Cancer Care Ontario (CCO) clinical practice guideline recommend the use of mpMRI before a repeat biopsy.[33,34] Our results corroborate these recommendations and are in favour of the use of targeted only biopsies in order to reduce the number of cores needed and potentially reduce biopsy-related side effects.

Despite high sensitivity and specificity for the detection of csPCa using mpMRI,[15-18] several limitations need to be discussed. In our study, Likert scores of 2 and 3 were associated with a 22.2% and 38% of Gleason score 7 or more, respectively. On the other hand, Likert scores 4 and 5 were associated with a 62.6% and 55.8% of Gleason score 7 or more detection rate, respectively, as already described in other studies;[11,12,14] however, the rate of negative biopsy in the Likert 4 and 5 MRI lesions was high, due to inadequate MRI readings and/or biopsy targeting. There are several scales currently in use to attribute a level of suspicion of mpMRI lesions. The most recent, not used in this study, is the Prostate Imaging – Reporting and Data System (PI-RADS) version 2,[35] which comprises an ordinal scale with range from 1–5. As for the Likert score, a PI-RADS score of 1–2 report the absence of suspicious lesion, while a PI-RADS score of 4 and 5 report a high or very high suspicion of clinically significant disease. PI-RADS 3 score reflect more indeterminate nature of the suspicious lesion. The use of a Likert score is based mainly on experience and may reflect a more subjective assessment than the standardized PI-RADS score. In our study, discrepancy between mpMRI imaging quality performed in several radiology centres may have played a role in the relatively high rate of csPCa detection in the Likert score 2 and 3 group of men compared to other studies,[11-15] as in the high negative rate of cancer detection in the Likert 4 and 5 groups. Due to the absence of standardization of the MRI exams in our study, a compromise between MRI report and our own reading of outside exams has been made. We decided to give the higher score on suspicious areas, like a score 3 on a Likert 2/3 or a score 4 on a Likert 3/4, explaining why we did biopsy on Likert 2 lesions and why the number of Likert 4 and 5 were high. This could be an explanation for an upstaging of MRI lesions and the high rate of negative targeted biopsies in the Likert 4 and 5 lesions that we found in our results. In a recent study, a comparison of initial and tertiary centre reads of mpMRI has shown a disagreement in 54% of the cases between readers, with a significant improvement in negative predictive

value and positive predictive value of the MRI followed by prostate biopsy for the second readings by subspecialized uroradiologists.[36]

In this study, the overall complication rate was 6.4%, with a urosepsis rate of 2.9%. There were more urosepsis in the SYS group (n=4) than in the TAR and TAR+SYS groups, but the numbers were low. Our complication rates corroborate the literature.[37]

This study has several limitations. The study population consisted of patients referred to a single institution and the results reflected the experience of a single operator, which could have introduced selection and result bias. The number of patients in each group was relatively low and may have impacted the results. The use of mpMRI from different centres did not allow for a standardization of the technique of MRI. Prostate mpMRI were read by an experienced urologist and radiologist, but the MRI-targeted biopsy, either by cognitive or MRI/US fusion, were done by a single urologist. The use of two different methods of TAR, cognitive and using the Urostation™ during the study may have impacted the precision of TAR. Finally, the use of a Likert score is no longer the standard for any ROI in a mpMRI, even though there has been no study showing the beneficial use of PI-RADS v2 over the Likert score to improve both sensitivity and specificity of mpMRI.

There are many factors influencing the results of studies looking at the use of mpMRI prior to prostate biopsy and the potential benefit of this intervention in terms of csPCa detection: 1) the population sampled, i.e., the benefit of TAR over SYS is confirmed in repeat-biopsy population, but more debatable in biopsy-naive patients; even so, the recent results from the PROMIS study are in favour of upfront MRI use in this population; 2) the definition of csPCa, which may differ in the literature, being the trigger for treatment decision, i.e., surveillance vs. intervention; 3) the quality of the imaging and of the reporting, even if efforts for standardization have been made; and most importantly 4) the accuracy of the needle placement in the target within the prostate gland.[38] Despite these limitations, the use of MRI prior to biopsy has shown, as in this study, that it could improve PCa detection.

Conclusion

The present study shows that MRI-targeted biopsy detected more men with clinically significant PCa and fewer men with clinically insignificant PCa than a systematic TRUS-guided biopsy in men after previous negative biopsy, with a lower number of biopsy cores. In biopsy-naive men, the addition of MRI-targeted biopsy to systematic biopsy increased the rate of csPCa detection significantly without adding more biopsy-related risk. These results need to be confirmed on a larger scale, but they are in favour of the role of mpMRI in the accuracy of csPCa diagnosis.

Competing interests: The authors report no competing personal or financial interests.

This paper has been peer-reviewed.

References

1. Canadian Cancer Society. Canadian Cancer Statistics publication. Available at http://www.cancer.ca/en/cancer-information/cancer-101/canadian-cancer-statistics-publication/?region=sk. Accessed August 7, 2017.
2. Eichler K, Hempel S, Wilby J, et al. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: A systematic review. *J Urol* 2006;175:1605-12. https://doi.org/10.1016/S0022-5347(05)00957-2
3. Djavan B, Ravery V, Zlotta A, et al. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: When should we stop? *J Urol* 2001;166:1679-83. https://doi.org/10.1016/S0022-5347(05)65652-2
4. Lecornet E, Ahmed H, Hu Y, et al. The accuracy of different biopsy strategies for the detection of clinically important prostate cancer: A computer simulation. *J Urol* 2012;188:974-80. https://doi.org/10.1016/j.juro.2012.04.104
5. Scattoni V, Zlotta A, Montironi R, et al. Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: A critical analysis of the literature. *Eur Urol* 2007;52:1309-22. https://doi.org/10.1016/j.eururo.2007.08.006
6. Bryant RJ, Sjoberg DD, Vickers AJ, et al: Predicting high-grade cancer at 10-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. *J Natl Cancer Inst* 2015;107. https://doi.org/10.1093/jnci/djv095
7. Villers A, Puech P, Mouton D, et al. Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumour volume: Correlation with radical prostatectomy findings. *J Urol* 2006;176:2432-7. https://doi.org/10.1016/j.juro.2006.08.007
8. Ahmed HU, Kirkham A, Arya M, et al. Is it time to consider a role for MRI before prostate biopsy? *Nat Rev Clin Oncol* 2009;6:197-206. https://doi.org/10.1038/nrclinonc.2009.18
9. Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion-targeted biopsy: A systematic review. *Eur Urol* 2015;68:8-19. https://doi.org/10.1016/j.eururo.2014.10.026
10. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): A paired validating confirmatory study. *Lancet* 2017;389:815-22. http://dx.doi.org/10.1016/S0140-6736(16)32401-1
11. Pokorny MR, De Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy vs. magnetic resonance (MR) imaging with subsequent mr-guided biopsy in men without previous prostate biopsies. *Eur Urol* 2014;66:22-9. https://doi.org/10.1016/j.eururo.2014.03.002
12. Siddiqui M, 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;313:390-7. https://doi.org/10.1001/jama.2014.17942
13. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer vs. systematic 12-core transrectal ultrasound biopsy. *Eur Urol* 2013;64:713-9. https://doi.org/10.1016/j.eururo.2013.05.059
14. Mozer P, Rouprêt M, Le Cossec C, et al. First round of targeted biopsies using magnetic resonance imaging/ultrasonography fusion compared with conventional transrectal ultrasonography-guided biopsies for the diagnosis of localized prostate cancer. *BJU Int* 2015;115:50-7. https://doi.org/10.1111/bju.12690
15. Kirkham AP, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate? *Eur Urol* 2006;50:1163-74; discussion 1175. https://doi.org/10.1016/j.eururo.2006.06.025
16. Wu LM, Xu JR, Ye YQ, et al. The clinical value of diffusion-weighted imaging in combination with T2-weighted imaging in diagnosing prostate carcinoma: A systematic review and meta-analysis. *AJR Am J Roentgenol* 2012;199:103-10. https://doi.org/10.2214/AJR.11.7634
17. Wu LM, Xu JR, Gu HY, et al. Usefulness of diffusion-weighted magnetic resonance imaging in the diagnosis of prostate cancer. *Acad Radiol* 2012;19:1215-24. https://doi.org/10.1016/j.acra.2012.05.016
18. Umbehr M, Bachmann LM, Held U, et al. Combined magnetic resonance imaging and magnetic resonance spectroscopy imaging in the diagnosis of prostate cancer: A systematic review and meta-analysis. *Eur Urol* 2009;55:575-90. https://doi.org/10.1016/j.eururo.2008.10.019
19. Wysock JS, Rosenkrantz AB, Huang WC, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: The PROFUS trial. *Eur Urol* 2013;66:343-51. https://doi.org/10.1016/j.eururo.2013.10.048

20. Ploussard G, Aronson S, Pelsser V, et al. Impact of the type of ultrasound probe on prostate cancer detection rate and characterization in patients undergoing MRI-targeted prostate biopsies using cognitive fusion. *World J Urol* 2014;32:977-83. https://doi.org/10.1007/s00345-013-1186-0
21. Rosenkrantz AB, Kim S, Lim RP, et al. Prostate cancer localization using multiparametric MR imaging: Comparison of Prostate Imaging Reporting and Data System (PI-RADS) and Likert scales. *Radiology* 2013;269:482-92. https://doi.org/10.1148/radiol.13122233
22. Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localization, and characterization of prostate cancer: Recommendations from a European consensus meeting. *Eur Urol* 2011;59:477-94. https://doi.org/10.1016/j.eururo.2010.12.009
23. Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of reporting for MRI-targeted biopsy studies (START) of the prostate: Recommendations from an international working group. *Eur Urol* 2013;64:544-52. https://doi.org/10.1016/j.eururo.2013.03.030
24. Ploussard G, Epstein JI, Montironi R, et al. The contemporary concept of significant vs. insignificant prostate cancer. *Eur Urol* 2011;60:291-303. https://doi.org/10.1016/j.eururo.2011.05.006
25. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review. *Eur Urol* 2013;63:125-40. https://doi.org/10.1016/j.eururo.2012.06.004
26. Emberton M. Has magnetic resonance-guided biopsy of the prostate become the standard of care? *Eur Urol* 2013;64:720-1. https://doi.org/10.1016/j.eururo.2013.06.050
27. Kasivisvanathan V, Dufour R, Moore CM, et al. Transperineal magnetic resonance image-targeted prostate biopsy vs. transperineal template prostate biopsy in the detection of clinically significant prostate cancer. *J Urol* 2013;189:860-6. https://doi.org/10.1016/j.juro.2012.10.009
28. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: Comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. *BJU Int* 2011;108:E171-8. https://doi.org/10.1111/j.1464-410X.2011.10112.x
29. 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; 313:390-7. https://doi.org/10.1001/jama.2014.17942
30. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review. *Eur Urol* 2013;63:125-40. https://doi.org/10.1016/j.eururo.2012.06.004
31. Borkowetz A, Platzek I, Toma M, et al. Comparison of systematic transrectal biopsy to transperineal magnetic resonance imaging/ultrasound-fusion biopsy for the diagnosis of prostate cancer. *BJU Int* 2015;116:873-9. https://doi.org/10.1111/bju.13023
32. Wu J, Ji A, Xie B, et al. Is magnetic resonance/ultrasound fusion prostate biopsy better than systematic prostate biopsy? An updated meta- and trial sequential analysis. *Oncotarget* 2015;6:43571-80. https://doi.org/10.18632/oncotarget.6201
33. National Institute for Health and Excellence (NICE). CG58 Prostate cancer: Diagnosis and treatment. Available at http://guidance.nice.org.uk/CG58/NICEGuidance/pdf/English. Accessed August 7, 2017.
34. Haider MA, Yao X, Loblaw A, et al. Evidence-based guideline recommendations on multiparametric magnetic resonance imaging in the diagnosis of prostate cancer: A Cancer Care Ontario clinical practice guideline. *Can Urol Assoc J* 2017;1:E1-7. https://doi.org/10.5489/cuaj.3968
35. PI-RADS(TM) Prostate Imaging – Reporting and Data System V.2. In.: American College of Radiology; 2015.
36. Hansen NL, Koo BC, Gallagher FA, et al. Comparison of initial and tertiary centre opinion reads of multiparametric magnetic resonance imaging of the prostate prior to repeat biopsy. *Eur Radiol* 2017;27:2259-66. https://doi.org/10.1007/s00330-016-4635-5
37. Loeb S, Vellekoop A, Ahmed HU, et al. Systematic review of complications of prostate biopsy. *Eur Urol* 2013;64:876-92. https://doi.org/10.1016/j.eururo.2013.05.049
38. Emberton M. Are men who are biopsied without prior prostate magnetic resonance imaging getting substandard care? *BJU Int* 2015;116:837-8. https://doi.org/10.1111/bju.13067

Correspondence: Dr. Franck Bladou, Department of Urology, Jewish General Hospital, McGill University, Montreal, QC, Canada; fbladou@jgh.mcgill.ca