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Research Article

Utility of multiple core biopsies during transperineal template-guided mapping biopsy for patients with large prostates and PI-RADS 1–2 on multiparametric magnetic resonance imaging

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ABSTRACT

Background: We investigated the necessity of multiple core biopsies when performing transperineal template-guided mapping biopsy (TTMB) for patients with large prostates and no suspicious lesions on multiparametric magnetic resonance imaging (mpMRI).

Materials and methods: We retrospectively analyzed 304 patients on active surveillance (AS), 212 patients with previously negative transrectal ultrasound-guided biopsy (TRUS-Bx) and 67 biopsy naïve patients who underwent TTMB between May 2017 and December 2020. The number of core biopsies and acute urinary retention (AUR) rates were analyzed in relation to the prostate volume (PV). Cancer detection rate according to the prostate volume and Prostate Imaging-Reporting and Data System (PI-RADS) scores were compared using the Pearson Chi-square test.

Results: AUR occurred more frequently in patients with PV over 39 cc (5.5% vs. 24.4%, $P < 0.001$). In addition, incidence of AUR was more in patients with PV over 39 cc and PI-RADS score of 1–2 on mpMRI (3.7% vs. 22.2%, $P < 0.001$). There was no significant difference in the detection rates of any prostate cancer or clinically significant prostate cancer (csPCA) between the patients on AS with PV < 39 cc and PV ≥ 39 cc and PI-RADS score 1–2 (57.4% vs. 50%, $P = 0.507$; 17% vs. 8.8%, $P = 0.412$, respectively). Additionally, no significant difference was found in the detection rates of any prostate cancer or csPCA between the patients with PV < 39 cc and PV ≥ 39 cc and PI-RADS score 1–2 who either had a previously negative TRUS-Bx or were biopsy naïve (27.9% vs. 16.2%, $P = 0.101$, 8.2% vs. 4.1%, $P = 0.31$, respectively).

Conclusion: Increasing the number of core biopsies of prostates measuring ≥39 cc with PI-RADS 1–2 on mpMRI does not significantly increase the detection rates of any prostate cancer or csPCA.

1. Introduction

Consensus exists among the guidelines on prostate cancer published by many urological societies, such as the European Association of Urology, European Association of Nuclear Medicine, European Society for Radiotherapy and Oncology, European Society of Urogenital Radiology, and International Society of Geriatric Oncology, regarding no definite role of transperineal template-guided mapping biopsy (TTMB).[1] However, there are studies that suggest that TTMB may be effective and useful in some cases as it can help in cancer detection, is not restricted by cancer location, and has fewer complications such as infections after biopsy when compared with the conventional transrectal ultrasound-guided biopsy (TRUS-Bx).[2–7] Therefore, TTMB is now widely utilized clinically. However, it is known that acute urinary retention (AUR) is higher in TTMB than in TRUS-Bx.[4,7,8] Factors such as age, prostate volume (PV), and number of core biopsies (NB) reportedly increase the risk of AUR after TTMB.[7,9]

Multiparametric magnetic resonance imaging (mpMRI) has become an essential tool in the detection of prostate cancer.[1] There are studies that suggest that MRI-targeted biopsy is probably similar or even better at cancer detection than the conventional methods.[10,11] However, studies have indicated that mpMRI may show false-negative results and TTMB can detect cancers that are

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missed on mpMRI.[2,12] Therefore, these studies emphasize the utility of TTMB.

TTMB has advantages over TRUS-Bx because of its ability to obtain a large number of samples, as well as its more convenient approach. Therefore, generally, as the volume of the prostate increases, a greater NB is needed, according to the Ginsburg protocol.[13] A study suggests that biopsy density (the ratio of the number of biopsy specimens to PV) should be above a certain value for optimal cancer detection.[14]

For cancer detection, TTMB should be considered initially. However, complications after biopsy are not negligible. In particular, AUR is reported to occur most commonly, and its incidence is affected by the presence of certain factors, as mentioned above. Among these factors, the number of core biopsies is the only modifiable factor, and we questioned whether multiple core biopsies should be performed when no suspicious lesion is detected by mpMRI during TTMB for the patients with large prostates, despite knowing that it increases the risk of AUR. Therefore, we designed this study to investigate the necessity or the lack thereof for performing multiple core biopsies during TTMB for patients with large prostates and no suspicious lesion on mpMRI.

2. Materials and methods

2.1. Ethics approval

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2021-01-074), and the IRB waived the requirement for informed consent due to the retrospective nature of this study. All study protocols were performed in accordance with the principles of the Declaration of Helsinki.

2.2. Study population

TTMB was performed in 583 patients under general anesthesia by a urologist from May 2017 to December 2020. Altogether, 304 active surveillance (AS) patients, 212 patients with previously negative TRUS-Bx, and 67 biopsy naïve patients were analyzed. In our institution, AS is performed for patients with very low-risk prostate cancer and selectively for those with low and intermediate-risk prostate cancer who have a favorable prognosis.

2.3. Biopsy protocol

TTMB was performed for patients with persistently elevated or increasing prostate-specific antigen (PSA) levels despite previously negative TRUS-Bx. TTMB, rather than TRUS-Bx, was initially performed for the patients at a high risk of acquiring infections or those who had rectal problems. Most patients underwent 24 to 36 systematic biopsies depending on the amount of volume relative to the normal PV of 30 cc according to the Ginsburg protocol. Under the clinician's decision, the standard protocol was not observed in some patients. We performed an additional targeted biopsy depending on the mpMRI results.

2.4. Variables included in the study

Age, PSA levels, PV, NB, PSA density, and mpMRI results were analyzed. mpMRI images were analyzed according to the Prostate Imaging-Reporting and Data System version 2 (PI-RADS v2), and PI-RADS v2 score >3 was considered a valid predictor of prostate cancer in our study. After performing TTMB, the pathological findings and complications were reviewed.

2.5. Statistical analysis

Quantitative variables are presented as median (interquartile range) or mean (standard deviation [SD] or range), and qualitative variables are presented as absolute values (percentages). Descriptive statistics were applied for demographic variables. The student *t* test and Pearson's Chi-square test were used for comparing the means and proportions, respectively. All statistical analyses were performed using IBM SPSS for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Values of $P < 0.05$ were considered statistically significant.

We assumed that there was little to no difference in the detection rates of any prostate cancer and clinically significant prostate cancer (csPCA) depending on PV and NB if there was no suspicious lesion on mpMRI. At the same time, we also assumed that there was a significant difference in the occurrence of AUR depending on PV and NB. Therefore, we focused on comparing the abovementioned detection and occurrence rates.

3. Results

3.1. Enrollment and patients' characteristics

mpMRI was performed before TTMB. Of 583 patients, 65 were excluded from the study due to the following reasons. Three patients on AS did not undergo mpMRI, images of two patients had low quality and, those of two other patients were not reviewed by a radiologist. Two more patients did not undergo regular TTMB, while 47 patients with a previously negative biopsy and 8 biopsy naïve patients did not undergo mpMRI (Fig. 1). Therefore, 518 patients were included in the study. Patient demographics and clinical characteristics of all the patients, those on AS, those with previously negative biopsy, and biopsy naïve patients are shown in Table 1.

TTMB revealed that of all patients on AS, prostate cancer was not detected in 83 patients (28%), 137 patients (46.3%) were diagnosed with clinically insignificant prostate cancer (ciPCA), and 76 patients (25.7%) had csPCA. Of the patients with a previously negative biopsy, 45 patients (27.3%) were diagnosed with prostate cancer. Among them, 30 patients (18.2%) were reported as having ciPCA, and 15 patients (9.1%) had csPCA. Among the biopsy naïve patients, 17 patients (29.8%) were diagnosed with prostate cancer. In that group, 11 patients (19.3%) presented with ciPCA, while six patients (10.5%) had csPCA. Acute urinary retention (AUR) occurred in 44 patients (14.7%) on AS, 29 patients (17.6%) with a previously negative biopsy, and 2 patients (3.5%) who were biopsy naïve (Table 1).

3.2. Number of core biopsies and occurrence of AUR

Patients belonging to each category (AS, previously negative biopsy, and biopsy naïve) were divided into two groups based on the PV cutoff value of 39 cc, which was the mean value of PV for the patients on AS and the biopsy naïve patients. We investigated NB, AUR rate, and cancer detection rate for the two groups of each category. In patients with PV < 39 cc, template NB and total NB were 26 ± 4.4 and 26.8 ± 4.5, respectively. In patients with PV $\geq$ 39 cc, template NB and total NB were 35.3 ± 2.9 and 35.8 ± 3, respectively. In patients with PV $\geq$ 39 cc, and <39 cc, AUR occurred in 60 (24.4%), and 15 patients (5.5%), respectively. These differences were significant between the two groups ($P < 0.001$). Ninety patients (33.1%) with PV < 39 cc were performed additional target biopsies and 58 patients (23.6%) with PV $\geq$ 39 cc were performed additional target biopsies ($P < 0.017$). Forty (44.4%) of the 90 patients with PV < 39 cc diagnosed with prostate cancer, and 21 (36.2%) of the 58 patients

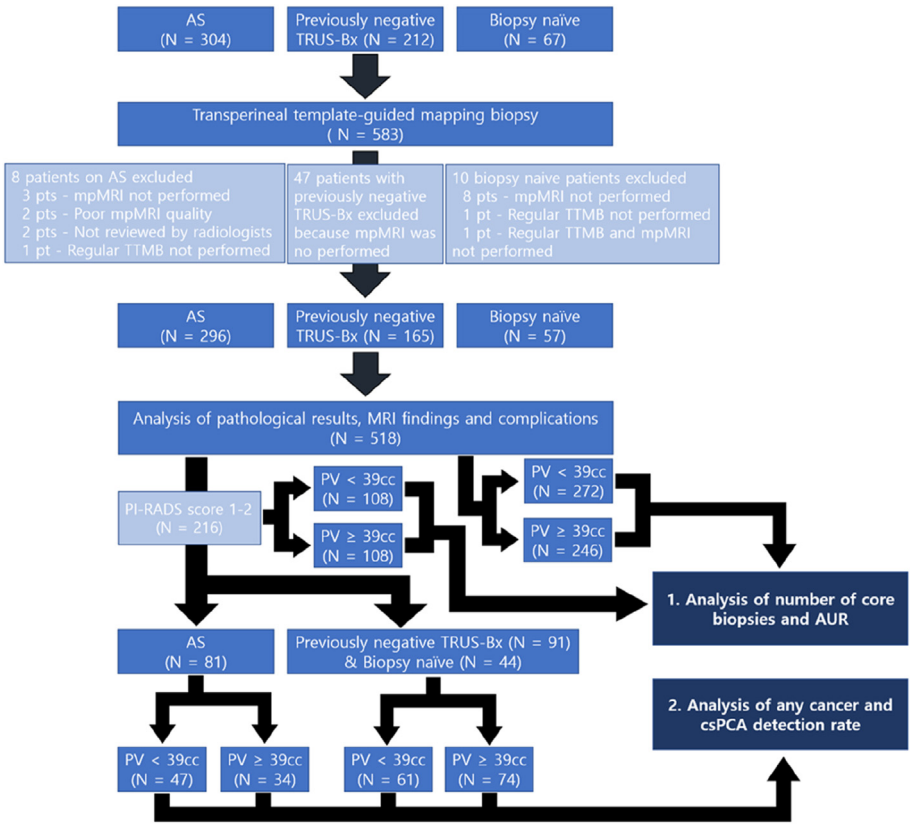

Fig. 1. Flowchart showing the distribution of the patients. AS, Active surveillance; AUR, Acute urinary retention; csPCA, clinically significant prostate cancer; mpMRI, Multi-parametric magnetic resonance imaging; PI-RADS, Prostate Imaging-Reporting and Data System; PV, Prostate volume; TRUS-Bx, Transrectal ultrasound-guided biopsy; TTMB, Template-guided mapping biopsy.

Table 1
Patients' characteristics

	Total ($N = 518$)	AS ($N = 296$)	Previously negative TRUS-Bx ($N = 165$)	Biopsy naïve ($N = 57$)
Age, years, mean ± SD	64.4 ± 7.9	65.9 ± 7.3	63.1 ± 7.1	60.1 ± 10.5
PSA, ng/mL, mean ± SD	7 ± 5.2	6 ± 3.8	9.4 ± 6.9	5.5 ± 2.6
Prostate volume, mL, mean ± SD	42.4 ± 21.1	38.8 ± 17.5	49.9 ± 25.7	39 ± 16.9
PSA density, ng/mL/mL, mean ± SD	0.18 ± 0.13	0.17 ± 0.13	0.2 ± 0.14	0.16 ± 0.08
Number of core biopsies, mean ± SD	31 ± 5.9	30.6 ± 5.9	32.3 ± 5.8	29.6 ± 6
PI-RADS score				
<3, n (%)	216 (41.7)	81 (27.4)	91 (55.2)	44 (77.2)
≥3, n (%)	302 (58.3)	215 (72.6)	74 (44.8)	13 (22.8)
≥4, n (%)	170 (32.8)	137 (46.3)	29 (17.6)	4 (7.0)
TTMB results				
Cancer absent, n (%)	243 (46.9)	83 (28)	120 (72.7)	40 (70.2)
Cancer present, n (%)	275 (53.1)	213 (72)	45 (27.3)	17 (29.8)
GS 3 + 3 = 6/10, n (%)	178 (34.4)	137 (46.3)	30 (18.2)	11 (19.3)
GS 3 + 4 = 7/10, n (%)	59 (11.4)	51 (17.2)	6 (3.6)	2 (3.5)
GS 4 + 3 = 7/10, n (%)	18 (3.5)	14 (4.7)	4 (2.4)	0 (0)
GS 4 + 4 = 8/10, n (%)	20 (3.9)	11 (3.7)	5 (3)	4 (7)
No. of positive cores, mean ± SD	4.1 ± 3.4	4.4 ± 3.5	2.7 ± 2.4	3.2 ± 3.1
Complications				
AUR, n (%)	75 (14.5)	44 (14.7)	29 (17.6)	2 (3.5)
Hematuria, n (%)	13 (2.5)	3 (1)	10 (6.1)	0 (0)
Hematospermia, n (%)	1 (0.2)	0 (0)	1 (0.6)	0 (0)
Prostatitis, n (%)	1 (0.2)	0 (0)	1 (0.6)	0 (0)

AS, Active surveillance; AUR, Acute urinary retention; GS, Gleason score; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, Prostate-specific antigen; SD, Standard deviation; TRUS-Bx, transrectal ultrasound-guided biopsy; TTMB, template-guided mapping biopsy.

with PV ≥ 39 cc were diagnosed with prostate cancer through additional target biopsies ($P = 0.03$) (Table 2).

In patients with PI-RADS scores of 1–2 on mpMRI, template NB was 26.2 ± 4.5 and 35.3 ± 2.8 in patients with PV < and >39 cc, respectively. The total NB was 26.1 ± 4.5 and 35.4 ± 2.8 in patients with PV < and >39 cc, respectively. These differences were also significant between the two groups ($P < 0.001$) (Table 2, Fig. 2).

Table 2
Number of core biopsies and occurrence of AUR according to the prostate size and PI-RADS score

Total				
	Total ($N = 518$)	Prostate volume <39 cc ($N = 272$)	Prostate volume ≥39 cc ($N = 246$)	*P*
Age, mean ± SD	64.4 ± 7.9	63 ± 8.6	65.9 ± 6.7	<0.001
Number of core biopsies				
Total number, mean ± SD, (range)	31 ± 6 (24–40)	26.8 ± 4.5 (24–40)	35.8 ± 3 (24 − 40)	<0.001
Template number, mean ± SD, (range)	30.4 ± 6 (24–38)	26 ± 4.4 (24–38)	35.3 ± 2.9 (24–38)	<0.001
Pts with additional target biopsies, n (%)	148 (28.6)	90 (33.1)	58 (23.6)	0.017
Patients with AUR, n (%)	75 (14.5)	15 (5.5)	60 (24.4)	<0.001
PI-RADS score 1–2				
	PI-RADS score 1–2			
	Total ($N = 216$)	Prostate volume <39 cc ($N = 108$)	Prostate volume ≥39 cc ($N = 108$)	*P*
Age, mean ± SD	62.3 ± 8.4	60.3 ± 8.7	64.3 ± 7.5	<0.001
Number of core biopsies				
Total number, mean ± SD, (range)	30.8 ± 5.9 (24–39)	26.2 ± 4.5 (24–36)	35.4 ± 2.8 (24–39)	<0.001
Template number, mean ± SD, (range)	30.7 ± 6 (24–36)	26.1 ± 4.5 (24–36)	35.3 ± 2.8 (24–36)	<0.001
Pts with additional target biopsy, n (%)	8 (3.7)	6 (5.6)	2 (1.9)	0.15
Patients with AUR, n (%)	28 (13)	4 (3.7)	24 (22.2)	<0.001

AUR, Acute urinary retention; PI-RADS, Prostate Imaging-Reporting and Data System; SD, Standard deviation.

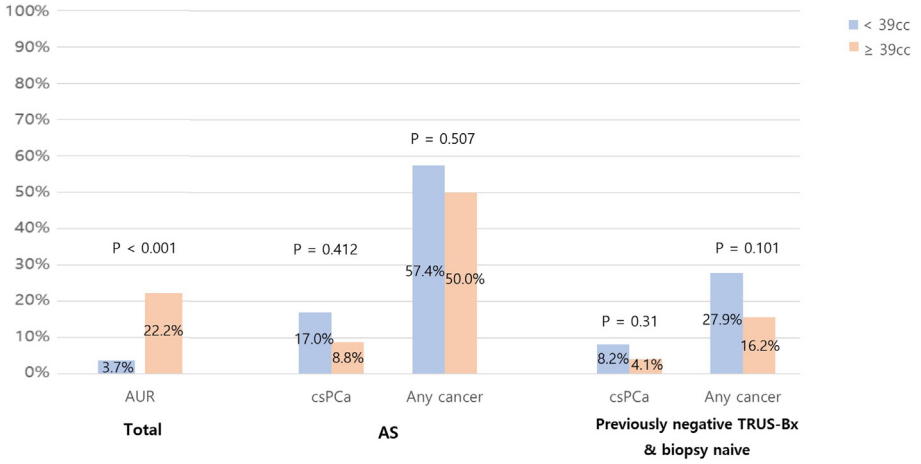

Fig. 2. Incidence of AUR and detection rate of csPCA and any cancer in patients with PI-RADS score 1-2 according to PV. AS, Active surveillance; AUR, Acute urinary retention; csPCA, clinically significant prostate cancer; PI-RADS, Prostate Imaging-Reporting and Data System; PV, Prostate volume; TRUS-Bx, Transrectal ultrasound-guided biopsy.

3.3. *Cancer detection rate*

TTMB revealed a higher detection rate for any prostate cancer in patients on AS and PI-RADS score of 1–2 with PV < 39 cc than in those with PV ≥ 39 cc, but this difference was not significant (57.6% vs. 50%, $P = 0.507$). In addition, patients with PV < 39 cc had a higher csPCA detection rate than those with PV ≥ 39 cc, but this was not a significant difference either (17% vs. 8.8%, $P = 0.412$) (Table 3, Fig. 2).

In the patients with previously negative TRUS-Bx and biopsy naïve patients with PI-RADS scores of 1–2, TTMB revealed that compared to patients with a PV > 39 cc, those with PV < 39 cc had a higher detection rate for any prostate cancer, as well as csPCA, although these differences were not significant (27.9% vs. 16.2%, $P = 0.101$; 8.2% vs. 4.1%, $P = 0.31$, respectively) (Table 3, Fig. 2).

4. Discussion

One of the biggest advantages of TTMB is its higher cancer detection rate when compared with TRUS-Bx.[2,3,5,6] In addition, research shows that TTMB can detect cancer that is not detected by mpMRI-targeted biopsy.[2,12] On the other hand, there are studies that have reported that TTMB carries a higher risk of AUR.[4,7,8] This means that an increased the cancer detection rate comes at a price of a higher incidence of AUR. However, our study suggests a way to lessen the AUR rate without affecting the cancer detection rate, and the utility of taking multiple core biopsies has not been studied much. Therefore, we believe that our study will help the clinicians in making a decision regarding the number of core biopsies that should be taken during TTMB.

In terms of the cancer detection rate following TTMB in the patients on AS, 79.4% of the patients on AS were diagnosed with cancer according to a study performed by Merrick et al. Among them, one-half of the patients had a Gleason score of 3 + 3, while the other half had a Gleason score ≥7.[15] Bhat et al. reported that 69.7% of the patients on AS were diagnosed with prostate cancer after TTMB.[16] In our study, cancer was detected in 72% of the patients on AS after TTMB, and among them, 64.3% of the patients had a Gleason score 3 + 3 and 35.7% the patients had a Gleason score of ≥7. Our study showed similar detection rates for prostate cancer and csPCA.

According to Hansen et al., 51.1% of the patients were diagnosed with cancer after transperineal guided targeted and 24-core systemic biopsy who had a previously negative TRUS-Bx. Among them,

Table 3
Cancer detection rate according to the prostate volume in patients with PI-RADS score 1–2

AS			
AS ($N = 81$)	PI-RADS Score 1–2		
	Prostate volume <39 cc	Prostate volume ≥39 cc	*P*
Number of patients, n (%)	47 (58)	34 (42)	
PSA, ng/mL, mean ± SD	4.4 ± 3.1	6.1 ± 4.1	0.031
PSA density, ng/mL/mL, mean ± SD	0.15 ± 0.12	0.11 ± 0.07	0.07
No. of biopsy cores, mean ± SD	27.1 ± 5.1	35.7 ± 2.1	<0.001
Cancer absent, n (%)	20 (42.6)	17 (50)	
Cancer present, n (%)	27 (57.4)	17 (50)	0.507
Gleason score 6, n (%)	19 (40.4)	14 (41.2)	
Gleason score 3 + 4, n (%)	7 (14.9)	2 (5.9)	0.412
Gleason score 4 + 3, n (%)	0 (0)	0 (0)	
Gleason score 8, n (%)	1 (2.1)	1 (2.9)	
Previously negative TRUS-Bx & biopsy naive			
Previously negative TRUS-Bx & Biopsy naïve ($N = 135$)	PI-RADS Score 1–2		
	Prostate volume <39 cc	Prostate volume ≥39 cc	*P*
Number of patients, n (%)	61 (45.2)	74 (54.8)	
PSA, ng/mL, mean ± SD	6.9 ± 3.4	8 ± 6.2	0.183
PSA density, ng/mL/mL, mean ± SD	0.2 ± 0.11	0.17 ± 0.1	0.075
No. of biopsy cores, mean ± SD	25.5 ± 3.8	35.2 ± 3.1	<0.001
Cancer absent, n (%)	44 (72.1)	62 (83.8)	
Cancer present, n (%)	17 (27.9)	12 (16.2)	0.101
Gleason score 6, n (%)	12 (19.7)	9 (12.2)	
Gleason score 3 + 4, n (%)	2 (3.3)	2 (2.7)	0.31
Gleason score 4 + 3, n (%)	1 (1.6)	1 (1.4)	
Gleason score 8, n (%)	2 (3.3)	0 (0)	

AS, Active surveillance; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, Prostate-specific antigen; SD, Standard deviation; TRUS-Bx, transrectal ultrasound-guided biopsy.

40.2% had a Gleason score of 3 + 3, and 59.8% had a Gleason score ≥7.[17] Similarly, Bittner et al. reported that 56.4% of these patients were diagnosed with prostate cancer after TTMB. Among them, 43.3% had a Gleason score of 3 + 3, and 56.7% had a Gleason score of ≥7.[18] In our study, prostate cancer was detected in 27.3% of such patients, after TTMB, who had a previously negative TRUS-Bx. Among them, 66.7% had a Gleason score of 3 + 3, and 33.3% had a Gleason score of ≥7. Our study showed lower detection rates for any prostate cancer, as well as csPCA. The difference between the results of this study and other studies is thought to be due to a racial factor. This study was conducted on the Asian population, and it is known that the PV of Asians is smaller than Westerners. This difference is thought to increase the biopsy density in the Asian population, and it might affect the result of previous systemic biopsy and TTMB.

According to Hansen et al., 69.8% of the patients on AS were diagnosed with prostate cancer; and csPCA was detected in 23.3% of these patients after TTMB when their Likert score was 1–2.[19] In our study, cancer was detected in 54.3% of the patients on AS, and 13.6% of these patients were diagnosed with csPCA after TTMB when PI-RADS score was 1–2. In addition, Hansen et al. reported that 24.2% of the patients with previously negative TRUS-Bx were diagnosed with cancer, and csPCA was detected in 8.8% of these patients after TTMB when their Likert score was 1–2.[19] In our study, 21.5% of the patients with previously negative TRUS-Bx and the biopsy naïve patients were diagnosed with cancer, and csPCA was detected in 5.9% of these patients after TTMB when PI-RADS score was 1–2. Therefore, the abovementioned results were similar for the two studies. In addition to these results, we performed further analysis by categorizing the patients based on PV.

Other studies report results that are similar to ours in terms of the occurrence of AUR. Kum et al.[9] reported an AUR rate of 12.8%, Muthuveloe et al.[20] 12.5%, Skouteris et al.[7] 7.9%, and Pepe and Aragona[21] reported an AUR rate of 6.7% after TTMB. Our study showed an AUR rate of 14.5%. According to Skouteris et al., those with PV greater than 42 cc had an AUR rate of 13.4% while the AUR rate was 2.7% for men with smaller prostates, and they suggested that larger PVs and a higher NB are probably associated with AUR.[7] In addition, Kum et al. suggested that PV and NB are the factors influencing AUR.[9] In our study, patients with PV greater than 39 cc had an AUR rate of 24.4% while the AUR rate for men with smaller prostates was 5.5%, and higher PV was related with higher NB. The AUR rate in our study is slightly higher when compared with those reported in other studies, but these results correlate with those of other studies in terms of suggesting a possible association between AUR rate, PV, and NB.

Targeted-biopsy can be used to reduce NB, and it can potentially decrease the AUR rate. Zhou et al. reported that magnetic resonance-guided prostate biopsy (MR-GPB) can reduce the rate of unnecessary prostate biopsies by approximately 30% and showed detection rates for any prostate cancer and csPCA that were comparable to those shown by TTMB. However, there was a limitation in its implementation because MR-GPB missed about a quarter of csPCA cases.[22] Furthermore, we cannot perform MR-GPB when there is no suspicious lesion on mpMRI, and thus, NB cannot be controlled. In this study, we focused on TTMB when there was no suspicious lesion on mpMRI, and analyzed the cancer detection rate in relation to NB.

According to Pham et al., there was no statistically significant difference in cancer upgrading or AUR rate between a 24-core TTMB and a more exhaustive TTMB in the patients on AS.[23] Although our study did not show whether cancer upgrading depended on NB, we were able to show that there was no statistically significant difference in the detection rates for any prostate cancer and csPCA between a 24-core and a 36-core TTMB if there was no suspicious lesion on mpMRI. In addition, our study showed that AUR was related to a large NB.

This study has some limitations. First, we did not take different NBs based on different PVs into consideration because we follow the Ginsburg protocol according to which 24 or 36 systematic

biopsies are performed depending on the value of PV relative to 30 cc. Second, this study analyzed a relatively small quantity of data. In particular, the number of biopsy naïve patients was so small that we could not extract significant results from this group. Despite these limitations, our study suggests a feasible biopsy method when TTMB is performed for the patients with large prostates and no suspicious lesion on mpMRI. In conclusion, there was no significant difference in any cancer detection rate between patients with PV < 39 cc and prostate volume ≥39 cc regardless of AS or previous negative biopsy and biopsy naive in PI-RADS score 1–2 on mpMRI. In addition, there was no significant difference in csPCA detection rate between patients with PV < 39 cc and prostate volume ≥39 cc regardless of AS or previous negative biopsy and biopsy naive in PI-RADS score 1–2 on mpMRI. Therefore, we do not need to take more NB for patients with large PV if there is no suspicious lesion on mpMRI. Further prospective randomized trials are required to determine the optimal indication for TTMB.

Author contributions

C.U.L. and H.G.J. contributed to conceptualization and writing - original draft. Data curation was performed by J.H.C., W.S., M.K., H.H.S., B.C.J., S.I.S., S.S.J. and H.M.L. Formal analysis was performed by C.U.L. Writing – review and editing was contributed to C.U.L. and H.G.J.

Conflicts of interest

The authors declare that there is no conflict of interests for the publication of this article.

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