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Sextant Systematic Biopsy Versus Extended 12-Core Systematic Biopsy in Combined Biopsy for Prostate Cancer

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ABSTRACT

Background: This study assessed the comparative effectiveness of sextant and extended 12-core systematic biopsy within combined biopsy for the detection of prostate cancer.
Methods: Patients who underwent combined biopsy targeting lesions with a Prostate Imaging Reporting and Data System (PI-RADS) score of 3–5 were assessed. Two specialists performed all combined cognitive biopsies. Both specialists performed target biopsies with five or more cores. One performed sextant systematic biopsies, and the other performed extended 12-core systematic biopsies. A total of 550 patients were analyzed.
Results: Cases requiring systematic biopsy in combined biopsy exhibited a significant association with age ≥ 65 years (odds ratio [OR], 2.32; 95% confidence interval [CI], 1.25–4.32; $P = 0.008$), PI-RADS score (OR, 2.32; 95% CI, 1.25–4.32; $P = 0.008$), and the number of systematic biopsy cores (OR, 3.69; 95% CI, 2.11–6.44; $P < 0.001$). In patients with an index lesion of PI-RADS 4, an extended 12-core systematic biopsy was required (target-negative/systematic-positive or a greater Gleason score in the systematic biopsy than in the targeted biopsy) ($P < 0.001$).
Conclusion: During combined biopsy for prostate cancer in patients with PI-RADS 3 or 5, sextant systematic biopsy should be recommended over extended 12-core systematic biopsy when an effective targeted biopsy is performed.

Keywords: Prostate Cancer; Diagnosis; Biopsy

INTRODUCTION

Prostate biopsy is required for a definitive diagnosis of prostate cancer (PCa). Since the recommendation of random systematic biopsy in 1980,[1] the standard method, characterized by transrectal ultrasound (TRUS) guided extended 12-core biopsy, has remained largely unchange.[2] However, this 12-core systematic biopsy could miss the diagnosis of clinically significant PCa and increase the diagnosis of insignificant PCa.[3,4]

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Chung JH, Park BK. Data curation: Chung JH. Formal analysis: Chung JH. Investigation: Chung JH. Methodology: Chung JH, Song W, Kang M, Sung HH, Jeon HG, Jeong BC, Seo SI, Jeon SS, Lee HM, Park BK. Project administration: Chung JH, Park BK. Resources: Song W, Kang M, Sung HH, Jeon HG, Jeong BC, Seo SI, Jeon SS, Lee HM, Park BK Validation: Chung JH. Visualization: Chung JH. Writing - original draft: Chung JH. Writing - review & editing: Park BK.

The effectiveness of pre-biopsy multiparametric magnetic resonance imaging (mpMRI) of the prostate has emerged.[5,6] A targeted biopsy, which is performed on the index lesion of pre-biopsy mpMRI, was suggested, which could increase the detection rate of clinically significant PCa.[7-9] However, in a meta-analysis, the detection rate of overall PCa did not differ between targeted and systematic biopsies.[10] Subsequently, a combined biopsy was proposed, in which both a systematic biopsy and a targeted biopsy for the index lesion were performed simultaneously. The effectiveness of pre-biopsy mpMRI-based combined biopsy in diagnosing PCa has been reported in a well-designed large-scale study.[11] In a systematic review, Wegelin et al.[12] reported that performing targeted biopsy without including systematic biopsies resulted in the omission of 19% of PCa cases, including 10% of clinically significant PCa cases. Moreover, most cribriform tumors were invisible on mpMRI, and combined biopsy increased the detection of cribriform morphology compared with targeted biopsy alone.[13] In a combined biopsy of the prostate, the index lesion is determined as the one with the highest Prostate Imaging Reporting and Data System (PI-RADS) score, and a targeted biopsy is performed accordingly.[14] In addition, a systematic biopsy is performed to improve the PCa detection rate (CDR) in combined biopsy.[15]

Several studies have investigated the best strategy for targeted biopsy among combined biopsies for PCa detection. According to the American Urological Association, more than two targeted biopsy cores are needed to detect PCa.[16] In the PRECISION trial, four targeted biopsy cores were recommended for diagnosing PCa.[9] According to Tu et al.,[17] more than four target biopsy cores showed a significantly greater CDR. Moreover, Chung et al.[18] recently reported that five or more target cores could reduce the underestimation of PCa. Although the number of target biopsy cores varies according to the clinician, multiple samplings may be needed, including a peripheral biopsy of the index lesion.

The necessity for systematic biopsy during combined biopsy has been studied.[19,20] Almost all previous studies conducted 12-core systematic biopsy in combined biopsy. However, the methodological aspects of this procedure have not been studied. In a combined biopsy, a 14-core biopsy should be performed along with an additional traditional extended 12-core systematic biopsy during targeted biopsy when performing a multicore saturation targeted biopsy for index lesions. Regarding multicore targeted biopsies, including the peripheral site of the index lesion and the high CDR of mpMRI-based targeted biopsies, the necessity of routine 12-core systematic biopsy in a combined prostate biopsy should be considered. Moreover, an escalating number of biopsy cores heightens the risk of biopsy-related complications, such as bleeding and inflammation, and unavoidably increases patient discomfort and distress.

When a targeted biopsy is effectively performed, the CDR of an additional sextant systematic biopsy might be non-inferior to that of a 12-core systematic biopsy in certain cases. Therefore, we hypothesized that a case in which the CDR of a six-core systematic biopsy was non-inferior to that of a 12-core combined biopsy would demonstrate that this method could reduce pain, suffering and biopsy-related complications in patients. Therefore, this study compared the efficacy of an additional sextant systematic biopsy with that of an extended 12-core systematic biopsy during a combined biopsy.

METHODS

Patients

We reviewed the records of 878 patients who underwent TRUS guided cognitive combined biopsy for PCa between June 2020 and December 2021. The biopsies were performed by two specialists (Prof. JH Chung and Prof. BK Park). Before 2020, Prof. JH Chung routinely performed extended 12-core systematic biopsy for a combined biopsy (these patients comprised the 12-core group), while Prof. BK Park performed sextant systematic biopsy for a combined biopsy (the six-core group). Specialists used the same methodology to perform targeted biopsies in combined biopsies. Although this was a retrospective study, the two specialists planned to conduct personal biopsy strategies without any modification prior to the study.

The study included patients with index lesions featuring a PI-RADS score of 3–5 per pre-biopsy mpMRI and those who underwent a combined biopsy conducted by one of the two specialists. Patients were excluded if they did not undergo a combined biopsy or, pre-biopsy mpMRI had no index lesions with a PI-RADS score of 3–5 on pre-biopsy mpMRI, underwent a clinically confirmatory biopsy for locally advanced PCa, had already been diagnosed with PCa, or if the specialist did not follow their biopsy strategies.

The necessity of systematic biopsy was considered in the following two cases: 1) when PCa was not diagnosed using targeted biopsy but by systematic biopsy only (target-negative/systematic-positive) and 2) when the Gleason score of systematic biopsy was greater than that of targeted biopsy (targeted < systematic, Gleason score).

Clinicopathological parameters

The baseline characteristics of the patients were evaluated, including age at biopsy, familial history, 5α-reductase inhibitor administration, prostate-specific antigen (PSA) level, prostate volume (measured using mpMRI), and history of prostate biopsy. mpMRI was used to assess the PI-RADS, index lesion size, index lesion location, PCa diagnosis, and Gleason score.

mpMRI-based combined biopsy

mpMRI was performed using a 3.0-tesla MRI scanner with a pelvic phased-array coil and without an endorectal coil. T2-weighted, diffusion-weighted, and dynamic contrast-enhanced (DCE) sequences were acquired according to the minimum standards set by consensus guidelines.[21] mpMRI was analyzed by uroradiologists using PI-RADS version 2.1.[6]

The two specialists performed targeted biopsies in the same manner. In the case of solitary target lesions, a six-core target biopsy (each including two centers and four peripheral biopsies) was performed. In cases with multiple target lesions, at least two cores were collected for the index lesions, and one or two additional cores were collected for each target lesion. Systematic biopsy was performed in areas other than the target lesions. However, a systematic biopsy is routinely performed when target lesions cannot be avoided (standard sextant biopsies were obtained at the base, mid, apex, and bilaterally, while extended 12-core were acquired at the base medial, mid medial, apex medial, base lateral, mid lateral, apex lateral, and bilateral).[22,23] All biopsies were performed using the transrectal approach.

Statistical analysis

The groups were compared using Fisher's exact test and the chi-squared test for categorical variables, and the Wilcoxon rank sum test for continuous variables. Logistic regression

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analysis was performed to evaluate the factors affecting the PCa diagnosis rate. Statistical analyses were performed using SPSS® (version 21.0) and R 3.6.1 (Vienna, Austria; http://www.R-project.org). Statistical significance was set at *P* values < 0.05.

Ethics statement

This study was performed in accordance with the applicable laws, regulations, good clinical practices, and ethical principles described in the Declaration of Helsinki. The Institutional Review Board (IRB) of the Samsung Medical Center approved this study (IRB No. 2022-11-137). The requirement for informed consent was waived owing to the retrospective nature of the study.

RESULTS

Two specialists performed prostate biopsies on 878 patients and analyzed the data of 550 patients; 142 patients who met the exclusion criteria and 186 who did not undergo a combined biopsy were excluded (**Fig. 1**).

Targeted biopsy with sextant systematic biopsy was performed in 340 (six-core group) of the 550 patients, and targeted biopsy with extended 12-core systematic biopsy was performed in 210 patients (12-core group). PCa was diagnosed in 30.6% and 53.8% of the patients in the six-core and 12-core groups, respectively. Patients diagnosed with PCa by systematic biopsy alone and not by targeted biopsy comprised 6.8% of the six-core group and 22.7% of the 12-core group (**Fig. 2**).

The nodule was palpable on digital rectal examination in 17.6% and 9.0% of the patients in the 12-core and in the six-core groups, respectively ($P = 0.004$). The mean PSA level was 6.59 ± 3.90 ng/mL in the 12-core group and 5.41 ± 3.76 ng/mL in the six-core group ($P < 0.001$), and the mean prostate volume was 40.15 ± 20.14 mL in the 12-core group and 45.63 ± 20.53

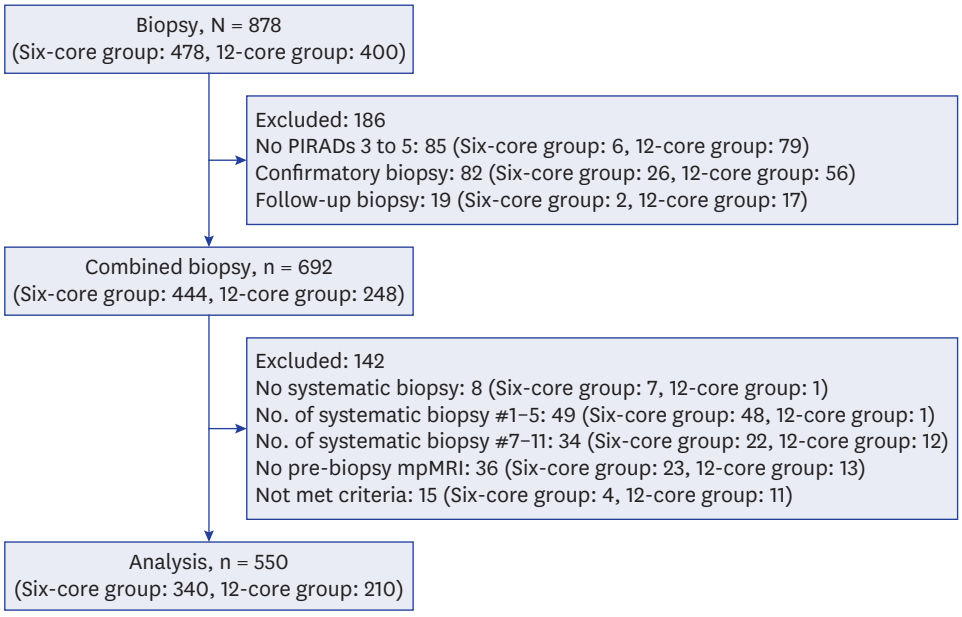

Fig. 1. Flow chart.
PIRADS = prostate imaging–reporting and data system, mpMRI = multiparametric magnetic resonance imaging.

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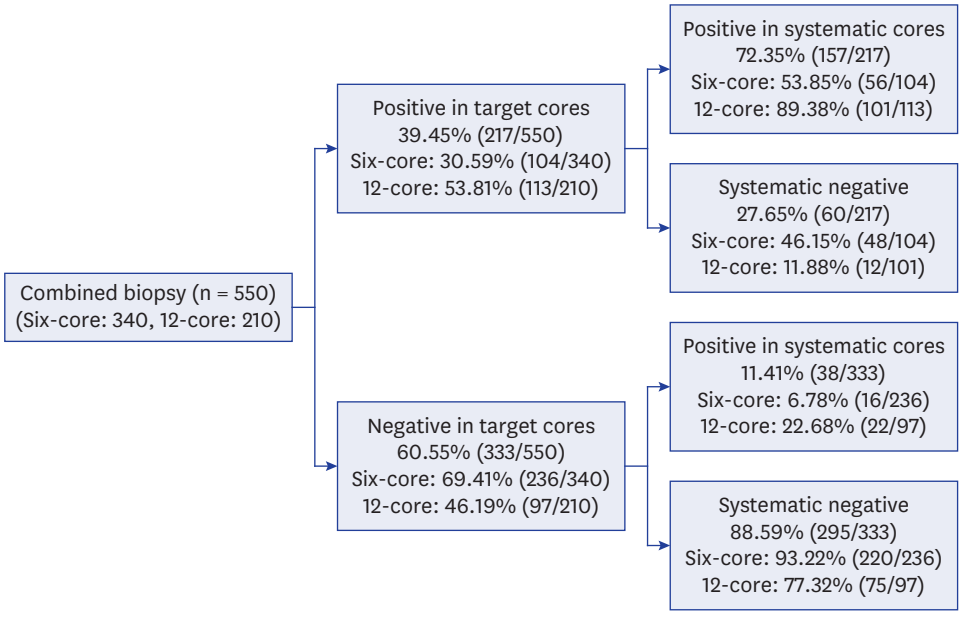

Fig. 2. Comparison of pathologic outcomes between two methods (six-core versus 12-core).

mL in the six-core group ($P < 0.001$). Index lesions were identified using mpMRI in 34.3% of patients with PI-RADS 3, 50.5% with PI-RADS 4, 15.2% with PI-RADS 5 in the 12-core group, and 66.8% with PI-RADS 3, 28.8% with PI-RADS 4, and 4.4% with PI-RADS 5 in the six-core group ($P < 0.001$) (**Table 1**).

Multivariate logistic regression analysis revealed no significant difference between the six-core and 12-core groups in PCa detection by targeted biopsy ($P = 0.266$). When PCa was

Table 1. Baseline characteristics

Variables	12 cores (n = 210)	6 cores (n = 340)	*P* value
Age, yr	66.10 ± 7.62	66.91 ± 7.42	0.301
Familial history	9 (4.29)	11 (3.24)	0.523*
5ARI administration	19 (9.05)	34 (10.00)	0.713*
No. of previous biopsy	0.22 ± 0.55	0.39 ± 0.74	0.005
DRE nodule	37 (17.62)	27 (9.03)	0.004*
PSA, ng/mL	6.59 ± 3.90	5.41 ± 3.76	< 0.001
Prostate volume, mL	40.15 ± 20.14	45.63 ± 20.53	< 0.001
PIRADS			< 0.001*
PIRADS 3	72 (34.29)	227 (66.76)	
PIRADS 4	106 (50.48)	98 (28.82)	
PIRADS 5	32 (15.24)	15 (4.41)	
Size of index tumor, cm	1.22 ± 0.50	1.25 ± 0.51	0.692
Location of index lesion			0.518†
Peripheral zone	135 (64.90)	218 (64.69)	
Transitional zone	71 (34.13)	116 (34.42)	
Central zone	2 (0.96)	1 (0.30)	
Overlapped	0 (0.00)	2 (0.59)	
Complications	3 (1.43)	8 (2.35)	0.452†
Acute urinary retention	2 (0.96)	2 (0.59)	
Acute prostatitis	1 (0.48)	6 (1.76)	
No. of target lesions	1.28 ± 0.49	1.44 ± 0.62	0.002

Values are presented as number (%) or mean ± standard deviation.
5ARI = 5-alpha reductase inhibitors, DRE = digit rectal examination, PSA = prostate specific antigen, PIRADS = prostate imaging–reporting and data system.
Wilcoxon rank sum test, *Chi-squared test, †Fisher's exact test.

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Table 2. Detection of prostate cancer, multivariable logistic regression analysis

Variables	Target biopsy		Systematic biopsy		Combined biopsy	
	Odd ratio	*P* value	Odd ratio	*P* value	Odd ratio	*P* value
Age	1.05	< 0.001	1.05	0.003	1.07	< 0.001
Familial history	2.07	0.208				
5ARI administration	0.59	0.240				
Previous biopsy	0.53	0.002	0.63	0.028	0.62	0.011
DRE nodule	1.52	0.245	1.52	0.255	1.63	0.203
PSA	1.07	0.040	1.08	0.012	1.06	0.063
Prostate volume, mL	0.96	< 0.001	0.96	< 0.001	0.96	< 0.001
PIRADS						
PIRADS 3	Reference		Reference		Reference	
PIRADS 4	4.94	< 0.001	3.42	< 0.001	5.29	< 0.001
PIRADS 5	7.36	< 0.001	10.62	< 0.001	10.85	< 0.001
No. of target lesions	0.88	0.544				
Group						
Six-core	Reference		Reference		Reference	
12-core	1.31	0.266	3.11	< 0.001	1.77	0.016

5ARI = 5-alpha reductase inhibitors, DRE = digit rectal examination, PSA = prostate specific antigen, PIRADS = prostate imaging–reporting and data system.

diagnosed by systematic biopsy, the odds ratio (OR) for CDR was 3.11 ($P < 0.001$) in the 12-core group compared to that in the six-core group; when diagnosed by combined biopsy, the OR for CDR was 1.77 in the 12-core group compared to that in the six-core group ($P = 0.016$) (**Table 2**).

Cases requiring systematic biopsy as part of combined biopsy (target-negative/systematic-positive or targeted < systematic biopsy, Gleason score) and CDR exhibited significant association with age ≥ 65 years (OR, 2.32; 95% confidence interval [CI], 1.25–4.32; $P = 0.008$), the PI-RADS score (OR, 2.32; 95% CI, 1.25–4.32; $P = 0.008$), and the number of systematic biopsy cores (OR, 3.69; 95% CI, 2.11–6.44; $P < 0.001$) (**Table 3**).

Table 3. Efficacy of systematic biopsy among combined biopsy, logistic regression analysis

Variables	Target (–), Systematic (+)		Target < systematic, Gleason score		Combined	
	Odd ratio	*P* value	Odd ratio	*P* value	Odd ratio	*P* value
Age	1.05	0.060	1.03	0.362	1.04	0.042
Age < 65 yr	Reference		Reference		Reference	
Age ≥ 65 yr	2.47	0.024	2.11	0.153	2.32	0.008
Familial history	0.00	0.986	0.66	0.692	0.40	0.382
5ARI administration	1.13	0.818	2.61	0.168	1.46	0.357
No. of previous biopsy	0.93	0.764	0.27	0.193	0.82	0.384
DRE nodule	2.54	0.066	1.13	0.820	1.64	0.174
PSA	1.04	0.279	0.98	0.692	1.02	0.615
Prostate volume	0.99	0.129	0.99	0.438	0.99	0.115
PIRADS						
PIRADS3	Reference		Reference		Reference	
PIRADS4	4.32	< 0.001	2.25	0.215	2.84	
PIRADS5	12.08	< 0.001	2.58	0.216	3.98	0.001
Size of index tumor	0.63	0.233	0.85	0.720	0.72	0.249
Location of index lesion						
Peripheral zone	Reference		Reference		Reference	
Transitional zone	0.65	0.252	0.45	0.167	0.58	0.083
Central zone			3.34	0.334	3.34	0.329
No. of target lesions	1.14	0.621	0.60	0.310	0.97	0.899
Six-core	Reference		Reference		Reference	
12-core	4.03	< 0.001	4.00	0.008	3.69	< 0.001

5ARI = 5-alpha reductase inhibitors, DRE = digit rectal examination, PSA = prostate specific antigen, PIRADS = prostate imaging–reporting and data system.

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Target (–), systematic (+)												
	Total		Age ≥ 65		Age < 65		PIRADS 3		PIRADS 4		PIRADS 5	
Variable	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value
Six-core	16 (6.78)		14 (9.59)		2 (2.22)		12 (6.12)		3 (8.33)		1 (25.00)	
12-core	22 (22.68)	0.0001	15 (30.00)	0.0008	7 (14.89)	0.0133	4 (7.69)	0.6826	14 (36.84)	0.0071	4 (57.14)	0.3167
Target < systematic, gleason score												
	Total		Age ≥ 65		Age < 65		PIRADS 3		PIRADS 4		PIRADS 5	
Variable	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value
Six-core	5 (4.81)		4 (5.88)		1 (2.78)		1 (3.23)		2 (3.23)		2 (18.18)	
12-core	19 (16.81)	0.0080	15 (20.00)	0.0190	4 (10.53)	0.2159	2 (10.00)	0.3395	14 (20.59)	0.0084	3 (12.00)	0.6235
Combined												
	Total		Age ≥ 65		Age < 65		PIRADS 3		PIRADS 4		PIRADS 5	
Variable	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value	Event, n (%)	*P* value
Six-core	21 (6.18)		18 (8.41)		3 (2.38)		13 (5.73)		5 (5.10)		3 (20.00)	
12-core	41 (19.52)	< 0.0001	30 (24.00)	0.0001	11 (12.94)	0.0068	6 (8.33)	0.4322	28 (26.42)	0.0002	7 (21.88)	0.8836

Fig. 3. Univariable logistic regression comparing six-core and 12-core systematic biopsies in combined biopsy.
PIRADS = prostate imaging reporting and data system.

Univariate logistic regression analysis was conducted to evaluate the effects of age and PI-RADS on the CDR in the six-core and 12-core groups. In the case of target-negative (-) and systemic positive (+) PI-RADS 4 lesions, the 12-core group had a significantly improved CDR, regardless of age ($P = 0.007$). In the 12-core group, age ≥ 65 years ($P = 0.019$) and PI-RADS 4 score ($P = 0.008$) were significantly associated with higher Gleason scores in systematic biopsies than in targeted biopsies. Overall, in patients with an index lesion of PI-RADS 4, a 12-core systematic biopsy was required (target negative [-], systematic positive [+], or target biopsy Gleason score < systematic biopsy Gleason score) ($P < 0.001$) (**Fig. 3**).

DISCUSSION

This study shows that, among combined prostate biopsies, if a targeted biopsy is performed, systematic biopsies could be reduced to six cores instead of 12 cores in PI-RADS 3 or 5 without inferior CDR.

Combined biopsy (targeted biopsy with 12-core systematic biopsy) is also strongly recommended because of its increased CDR by approximately 10% compared with a targeted biopsy alone.[11] In the present study, the CDR was 39.5% (217/550) for a targeted biopsy alone, with a 46.4% (255/550) improvement in diagnostic ability compared to that of a combined biopsy. Among the patients diagnosed by a systematic biopsy only rather than a targeted biopsy, 42.1% (16/38) were in the six-core group, and the remaining 57.9% (22/38) were in the 12-core group.

The extended 12-core systematic biopsy increased the CDR by approximately 20% compared to the sextant systematic biopsy when pre-biopsy mpMRI had not yet been popularized, and only systematic biopsy was performed.[24] Bjurlin et al.[25] suggested that a 12-core systematic prostate biopsy incorporating apical and far-lateral cores in the distribution template would

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allow maximal cancer detection and avoidance of repeat biopsy while minimizing the detection of insignificant PCa. In this study, regardless of the targeted biopsy results, the CDR for systematic biopsy was 22.4% (123/550) in the 12-core group and 13.1% (72/550) in the six-core group. However, we performed, systematic biopsy in region beyond the target lesions.

Although several studies have reported on the strategy of targeted biopsy in combined biopsy, the methodology of systematic biopsy in combined biopsy has not yet been reported. The number of target biopsy cores for index lesions in combined biopsies is increasingly recommended, ranging from at least two to more than 5 cores.[17,18,26,27] In addition to target biopsy. a combined biopsy requires systematic biopsy. Therefore, at least 14 biopsies or more cores were required for a combined biopsy. A higher number of biopsy cores increases the risk of complications, such as bleeding and inflammation, procedure time, pain, and patient suffering. Therefore, further research is required to improve the methodology of systematic biopsy for combined biopsies.

The effectiveness of systematic biopsy in combined biopsy is essential in two cases: 1) when PCa has been diagnosed by systematic biopsy and not by targeted biopsy and 2) when the systematic biopsy yields a higher Gleason score than the targeted biopsy. However, if the cancer risk is high, such as in PI-RADS 5 lesions,[28] collecting a large number of systematic biopsies holds less significance for PCa detection and its clinical implications. In this study, in the case of PI-RADS 3 or 5, systematic biopsy showed a significantly smaller effect on CDR compared to the six-core and 12-core groups. The high probability of PCa in PI-RADS 5 lesions and low probability of cancer in PI-RADS 3 lesions may reduce the necessity for many systematic biopsies in a combined biopsy.

The overall CDR in the combined biopsy of PI-RADS3 (27–29%) was lower than that of PI-RADS 4 (68%). Additionally, the CDR of PI-RADS5 is very high (86–88%).[29,30] In patients with had index lesion of PI-RADS 5, the CDR in target biopsy is very high; therefore, the significance of systematic biopsy might be reduced. Moreover, in patients with PI-RADS 3 index lesions, the significance of systematic biopsy would also be reduced, because the overall CDR is low inpatients with PI-RADS 3 index lesion. In this study, the overall CDR was 23.1% (69/299) for PI-RADS 3, 72.1% (147/204) for PI-RADS 4, and 87.2% (41/47) for PI-RADS 5. In addition, PCa diagnosed by systematic biopsy alone was 6.0% (18/299) in PI-RADS 3, 27.5% (56/204) in PI-RADS 4, and 10.6% (5/47) in PI-RADS 5 groups.

The major problem with mpMRI is the discordance between readers.[31] However, in this study, the mpMRI readings were obtained by experienced uro-radiologists. Classification between PI-RADS 3 and 4 was performed using diffusion-weighted images (DWI) and DCE images, and transition zone cancer was evaluated using T2 weighted images (T2WI). Therefore, DWI, T2WI and DCE were interpreted according to PI-RADS version 2.1 to interpret mpMRI. Considering the CDR for each lesion in this study, it is evident that there would have been no significant interference in the interpretation.

In addition, as a continuous variable, age was analyzed by determining the optimal cutoff based on Youden's index for classification (age, 64 years; sensitivity, 82.3%; specificity, 35.6%; Youden's index, 0.17914). When comparing the Gleason scores of patients aged < 65 years, the significance of systematic biopsy was related to the number of systematic biopsy cores. This finding may be attributed to the low risk of developing significant PCa at a relatively young age. However, for the CDR, the 12-core group was superior to the six-core group.

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Our analysis indicated that the CDR of the targeted biopsy was greater in the 12-core group than in the six-core group. Moreover, the baseline characteristics of the two groups were significantly different. However, the logistic regression analysis revealed that the CDRs of the targeted biopsies did not differ significantly between the two specialists. Therefore, no significant difference was observed in the ability of the two specialists to perform biopsies, and any difference between the groups could be attributed to the use of a systematic biopsy.

Cognitive biopsy uses mpMRI to identify an index prostate lesion and targets the index lesion under ultrasonographic guidance without using mpMRI fusion software or ultrasonography images. This technique is also known as a visually directed or cognitive biopsy. The operator performing the biopsy reviews the mpMRI to determine the location of the index lesion and then uses anatomic landmarks to correlate the lesion location to a site on the ultrasound images at biopsy.[32] In this study, prostate biopsies were performed cognitively. Several studies have reported that fusion biopsy is superior to cognitive biopsy in detecting significant cancer.[33-35] However, previous studies have not suggested targeted biopsy strategies. In the present study, to improve the CDR and Gleason score underestimation, a targeted biopsy with a large number of cores (approximately six cores), including index lesion peripheral biopsy, was performed to compensate for the weakness of cognitive biopsy.[18] In our previous study, we reported that a target biopsy of five cores or more, including the center of index lesion and peripheral tissues, can expect optimal CDR and avoid Gleason score underestimation.[18] In the present study, a mean of 5.96 core biopsy were performed on the index lesions.

In a meta-analysis, Schoots et al.[10] reported that the detection rates of overall and clinically significant PCa did not differ between cognitive and fusion prostate biopsy. Moreover, in a multicenter prospective study, detection of overall and clinically significant PCa did not differ between the two types of prostate biopsy, even when stratified by lesion location and volume.[36] Cognitive biopsy, in contrast to fusion biopsy, placed importance on the expertise of the individual conducting the procedure. The two specialists in this study, conducting > 250 combined prostate biopsies annually, encountered no cases where, targeting the index lesions on MRI was not feasible.

All biopsies were performed using the transrectal approach. Although the transperineal approach has a lower risk of infections such as prostatitis, its superiority in CDR has not been proven.[37] Moreover, in this era of combined biopsy, a comparison between the transperineal and transrectal approaches has still not been reported in a well-designed randomized controlled trial. In this study, there were no difficulties in targeting of the anterior or transitional zone index lesions.

This study was limited by its retrospective design. However, this bias was minimized by two specialists planning the concept prospectively, without changing their combined biopsy strategy. Another limitation was the relatively small number of patients included in the study. Additionally, pain scale scores and laboratory changes were not evaluated. A well-designed, large-scale prospective clinical trial is required to identify the optimal number of systematic biopsy cores for combined biopsy. Nevertheless, this study is the first to suggest a strategy to alleviate patient pain and suffering by reducing the number of cores in a combined biopsy without reducing the CDR.

In conclusion, when targeted biopsy is performed, a 12-core systematic biopsy should be performed in cases with PI-RADS 4 lesions for combined prostate biopsy. In cases of PI-

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RADS 3 or 5, a six-core systematic biopsy could be performed in combined biopsy without inferior outcomes to those of a 12-core systematic biopsy.

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