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Original Article

Targeted biopsy added to systematic biopsy improves cancer detection in prostate cancer screening

Peizi Li[1*], Pu Ni[2*], Faruk Erdem Kombak[1], Emily Wolters[1], George Kenneth Haines[1], Qiusheng Si[1]

[1]Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Department of Pathology, Mount Sinai West Hospital, New York, NY, USA. [*]Co-first authors.

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Abstract: Background: Magnetic resonance imaging (MRI)/ultrasound targeted biopsy has frequently been used together with a 12-core systematic biopsy for prostate cancer screening in the past few years. However, the efficacy of targeted biopsy compared to systematic biopsy, as well as its clinical-histologic correlation, has been assessed by a limited number of studies and is further investigated in this study. Design: We collected 960 cases with both targeted and systematic prostate biopsies from 04/2019 to 04/2022 (Table 1). We compared cancer detection rates between targeted and systematic prostate biopsies in different grade groups. Correlations with the size of prostate lesions, prostate-specific antigen (PSA) level, and Prostate Imaging-Reporting and Data System (PI-RADS) scale were also analyzed for each of these biopsy methods. Results: Among the 960 men who underwent targeted biopsy with systematic biopsy, prostatic adenocarcinoma was diagnosed in 652 (67.9%) cases. 489 (50.9%) cases were diagnosed by targeted biopsy and 576 (60.0%) cases were diagnosed by systematic biopsy. In the 384 cases diagnosed negative by systematic biopsy, targeted biopsy identified cancer in 76 (8%) cases. Systematic biopsy was able to detect 163 cancer cases that were missed by targeted biopsy. Systematic biopsy detected more grade group 1 cancers compared to targeted biopsy. However, for higher grade cancers, the differences between the cancer detection rates of targeted biopsy and systematic biopsy became negligible. Targeted biopsy upgraded the grade group categorized by systematic biopsy in several cases (3.8%, 7.0%, 2.6%, 1.1% and 0.9% in Grade Groups 1, 2, 3, 4, and 5 respectively). Targeted biopsy was more likely to detect cancer in larger lesions (13.17 mm VS 11.41 mm, P=0.0056) and for higher PI-RADS scales (4.19 VS 3.68, P<0.0001). The cancers detected by targeted biopsy also had higher PSA levels (10.38 ng/ml VS 6.39 ng/ml, P=0.0026). Conclusion: Targeted biopsy with systematic biopsy improved cancer detection rate compared to systematic biopsy alone. Targeted biopsy is not more sensitive for grade groups 1, 4, or 5 cancers but is as sensitive as systematic biopsy for detecting grade group 2 and 3 cancers. Targeted biopsy is more effective at detecting cancers when patients have larger lesions, higher PI-RADS scales, and higher PSA levels.

Keywords: Targeted biopsy, systematic biopsy, prostate cancer

Introduction

As one of the most prevalent cancers among men in the United States, prostate adenocarcinoma places a significant burden on the health system [1]. Prostate biopsy continues to play an important role in cancer detection and guiding management, serving as the mainstay of prostate cancer diagnosis [2]. The transurethral ultrasound-guided 12-core biopsy has long served as the conventional standard for detection, enabling nonbiased, spatially arranged sampling [3]. The standard biopsy, also known as systematic biopsy or random biopsy, involves sampling multiple areas of the prostate gland in a systematic manner. It is widely available and commonly performed in various healthcare settings, making it accessible to a large population of patients. It also has a well-established protocol for sampling different regions of the prostate gland, allowing for consistent comparison of results across various patients. However, systematic biopsy may cause sampling bias by missing small or clinically significant lesions, particularly if they are located in areas not routinely sampled or if they are not detectable by imaging. Systematic biopsy may also detect clinically insignificant cancers that do not require treatment, leading to overdiagnosis and overtreatment [4, 5]. Magnetic resonance

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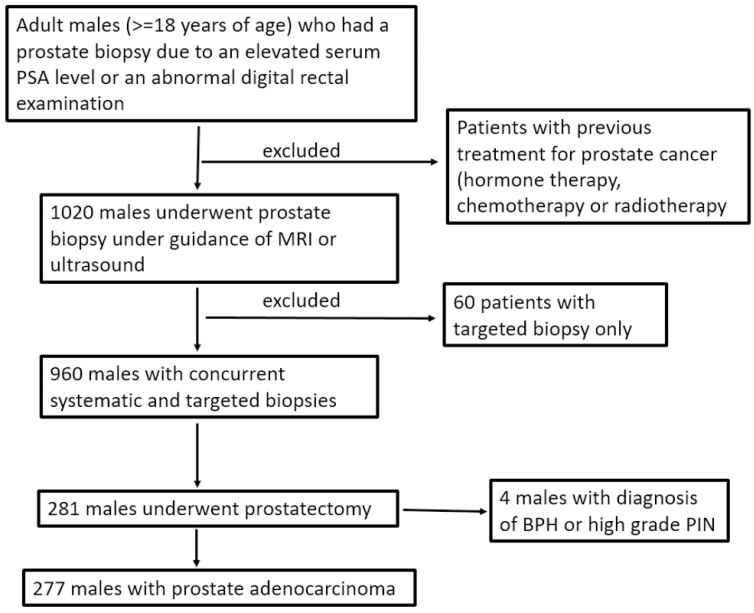

Figure 1. Enrollment and outcomes.

imaging (MRI)/ultrasound targeted biopsy has been used together with the 12-core systematic non-targeted biopsy for prostate cancer screening in the past few years [6, 7]. MRI or ultrasound guided targeted biopsy offers increased precision and may reduce overdiagnosis compared to systematic biopsy, but it requires specialized equipment and expertise [8, 9]. Compared to systematic biopsy, targeted biopsy is generally more expensive as it requires specialized imaging techniques [10, 11]. However, the targeted biopsy also has more sensitivity for detecting clinically significant prostate cancer, particularly in cases where lesions are small or located in challenging anatomic regions. The efficacy of targeted biopsy compared to systematic biopsy, as well as its clinical-histologic correlation, has only been assessed by a limited number of studies. Thus, we initiated a study at The Mount Sinai Health System to evaluate whether the use of transrectal ultrasound (TRUS) guided or MRI-guided targeted biopsy could replace the traditional systematic biopsy approach to efficiently and effectively diagnose prostatic carcinoma.

Methods

Study design

Adult males (≥18 years of age) who had an elevated serum prostate-specific antigen (PSA) level or an abnormal digital rectal examination were eligible to undergo prostate standard and targeted biopsies. Patients who consented to undergo a prostate biopsy were eligible for enrollment for the study. Exclusion criteria included previous treatment for prostate cancer (either hormone therapy, chemotherapy, or radiotherapy), patients with only targeted biopsy or 12-core standard/systematic biopsy rather than both, or the absence of an ultrasound/MRI visible lesion. We initially found 1020 patients who had undergone prostate biopsy in our health system from April 2019 to April 2022. After an initial screening, 60 patients who had only targeted biopsy were excluded. As a result, we included 960 patients who had concurrent systematic and targeted biopsies (**Figure 1**).

Prostate biopsy protocol

All included patients underwent both ultrasound-guided or MRI-targeted biopsy and systematic biopsies simultaneously at a single institution. The 12-core traditional/systematic/standard biopsy provides nontargeted, systematically spaced sampling of the prostate. In contrast, the MRI/ultrasound-guided biopsy samples 1-2 cores of the most suspicious area under MRI or ultrasound guidance. The patients in our cohort had concurrent targeted (usually 2-core) and systematic (12-core) prostate gland biopsies. Informed consent was waived for this study due to the retrospective and de-identified data collection with minimal risk. The protocol was approved by the Ethics Committee of Icahn School of Medicine at Mount Sinai (Project identification code: IF2814502).

Definitions of terms

The Gleason score is a grading system used to evaluate the aggressiveness of prostate cancer based on the microscopic appearance of cancer cells observed in a biopsy sample. The Gleason score is calculated by adding the Primary Gleason Grade (the grade of the most

predominant pattern observed in the biopsy sample) to the Secondary Gleason Grade (the grade of the second most predominant pattern observed.). The International Society of Urological Pathology definitions of grade groups are as follows: grade group 1 (Gleason score 3+3=6), grade group 2 (Gleason score 3+4=7), grade group 3 (Gleason score 4+3=7), grade group 4 (Gleason scores 4+4=8, 3+5=8, 5+3=8), grade group 5 (Gleason scores 4+5=9, 5+4=9, 5+5=10) [12, 13]. Gleason scores range from 6 (lowest grade of cancer) to 10 (highest grade of cancer) and are categorized into different cancer risk groups: low risk group (Gleason score of 6), intermediate risk group (Gleason score of 7) and high risk group (Gleason score of 8, 9, 10) [13, 14]. PI-RADS (Prostate Imaging-Reporting and Data System) is a structured reporting scheme for multiparametric prostate MRI in the evaluation of suspected prostate cancer in treatment naive prostate glands [15]. The Gleason score is an essential component of prostate cancer staging and is used in conjunction with other factors, such as PI-RADS, PSA levels and clinical stage, to determine the appropriate treatment approach, prognosis, and risk stratification for patients with prostate cancer [16-18].

Data collection

Patient clinical information, including age, PSA level, and PI-RADS score, was collected in a retrospective manner from the Mount Sinai internal pathology database and electronic health records from April 2019 to April 2022. Both targeted and systematic biopsies from each patient were assessed. For targeted biopsies, if multiple cores from the same targeted area in the same patient had tumor, we documented the core with the higher Gleason score. If they had the same Gleason score, we documented the core with a higher percentage of tissue involved by carcinoma. For the corresponding systematic biopsy, when there were locations reflecting the same area as a targeted biopsy, we documented the core with a higher Gleason score. If the systematic and targeted biopsy from the same location had the same score, we documented the core with a higher percentage of tissue involved by carcinoma. We also documented the systematic biopsy core with the highest Gleason score and its corresponding carcinoma size and percentage, if inconsistent with the targeted location. If there were multiple lesions with an available PI-RADS score, we recorded the score associated with the targeted area.

Statistical analysis

The primary hypothesis in our study was that prostate cancer detection rate is different between targeted and systematic prostate biopsies in different Gleason grade groups. The null hypothesis in this study is that there is no difference between cancer detection rates among targeted and systematic biopsies in different grade groups. The second hypothesis was that tumor size, PSA level, and/or PI-RADS score are statistically different between carcinomas detected by targeted biopsy and carcinomas missed by targeted biopsy but identified on systematic biopsy. When designating the PI-RADS and Gleason score, we arbitrarily designated a benign biopsy as a score of 0. In the targeted biopsy group, the cancer detection rate was calculated by dividing the number of group grade specific cases detected by targeted biopsy by the total number of grade group specific cases detected through both targeted and systematic biopsies. Similarly, the cancer detection rate for systematic biopsy was calculated using the same concept. Continuous variables were presented as median with range, or mean with standard error of the mean (SEM) as listed in the table. Categorical variables were recorded as counts and percentage. The two-tailed Student's t-test was performed when comparing two groups of means. One-way ANOVA with Tukey's post hoc test was used in three groups comparisons. A significant difference was determinedwhen the p-value was <0.05.

Results

General clinicopathologic features in targeted and systematic biopsy

960 male patients who had undergone concurrent targeted and systematic biopsies at our institution between 2019 to 2022 were included (**Table 1**). The median age of these patients was 66 year old, with a range from 26 to 88 years. There were 946 patients with a known PSA value before biopsy, and the mean level was 8.8 ng/ml. Of the 960 patients, 903 had a PI-RADS score with a mean value of 4. When

Table 1. General clinicopathologic features

	Demographics		
Age (median, range)	66 (26-88)		
PI-RAD (mean, SEM)	3.9 ± 0.03		
PSA (mean, SEM)	8.8 ± 0.4		
	Targeted Biopsy	Systematic Biopsy	*P*-value
Gleason Score (mean, SEM)	3.5 ± 0.1	4.1 ± 0.1	<0.01
Tumor Length (mm; mean, SEM)	18.0 ± 0.8	23.8 ± 1.0	<0.01
Tumor Percentage (mean, SEM)	6.4 ± 0.3	3.5 ± 0.2	<0.01

SEM = standard error of the mean.

Table 2. Grade group of each case identified by targeted biopsy was compared to systematic biopsy

		Targeted Biopsy						
		No cancer	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Systematic Biopsy	No cancer	308 (32.1%)	36 (3.8%)	25 (2.6%)	9 (0.9%)	4 (0.4%)	2 (0.2%)	384
	Grade 1	106 (11.0%)	81 (8.4%)	42 (4.4%)	4 (0.4%)	1 (0.1%)	0 (0.0%)	234
	Grade 2	37 (3.9%)	37 (3.9%)	76 (7.9%)	12 (1.3%)	3 (0.3%)	2 (0.2%)	167
	Grade 3	11 (1.1%)	9 (0.9%)	26 (2.7%)	26 (2.7%)	3 (0.3%)	1 (0.1%)	76
	Grade 4	7 (0.7%)	6 (0.6)	4 (0.4%)	27 (2.8%)	22 (2.3%)	4 (0.4%)	70
	Grade 5	2 (0.2%)	0 (0.0%)	4 (0.4%)	5 (0.5%)	5 (0.5%)	13 (1.4%)	29
	Total	471	169	177	83	38	22	960

Data in blue indicate concordance between targeted and systematic biopsy. Data in green show that targeted biopsy detected new tumors or upgraded the grade groups compared to systematic biopsy. Data in yellow indicate that targeted biopsy down-graded the grade groups compared to the systematic biopsy.

comparing Gleason scores between the targeted biopsies and standard systematic biopsies, mean Gleason scores were significantly lower in the targeted biopsy cores compared to systematic biopsy cores (3.5 vs 4.1, P<0.01, **Table 1**). When comparing the biopsy cores with the highest Gleason score, the carcinoma length was significantly greater in systematic biopsy with a mean measurement of 23.8 mm compared to 18.0 mm in targeted biopsy (P<0.01). However, the percentage of tissue in the core involved by carcinoma showed the opposite result, with a mean of 6.4% in targeted biopsy versus 3.5% in systematic biopsy (P<0.01). This could be attributed to the fact that targeted cores tended to be shorter than systematic cores. Of the 960 men who were enrolled in the analysis, 281 underwent subsequent prostatectomy. Of these 281 men, 277 were diagnosed with prostatic adenocarcinoma, and 4 were diagnosed with either benign prostatic hyperplasia (BPH) or high grade prostatic intraepithelial neoplasm (PIN) in the prostatectomy specimen. These four patients had very small focus of Grade group 1 carcinoma on biopsy, and pursued prostatectomy for symptomatic relief from BPH; which did not reveal residual carcinoma despite entire submission.

Cancer detection in targeted versus systematic biopsy

Among the 960 men who underwent concurrent targeted biopsy with systematic biopsy, prostatic adenocarcinoma was diagnosed in 652 (67.9%) cases. 489 (50.9%) cases were diagnosed by targeted biopsy and 576 (60.0%) cases were diagnosed by systematic biopsy. In the 384 negative cases diagnosed by systematic biopsy, targeted biopsy identified cancer in 76 (8.0%) cases. Targeted biopsy upgraded the grade group categorized by systematic biopsy across all grade groups (3.8%, 7.0%, 2.6%, 1.1% and 0.9% in Grade Groups 1, 2, 3, 4, and 5 respectively; **Table 2**).

Targeted biopsy is more effective at detecting cancers in certain conditions

The systematic biopsy method detected more grade group 1 carcinomas (100%; **Figure 2**). The targeted biopsy method demonstrated a slightly higher detection rate for grade group 2

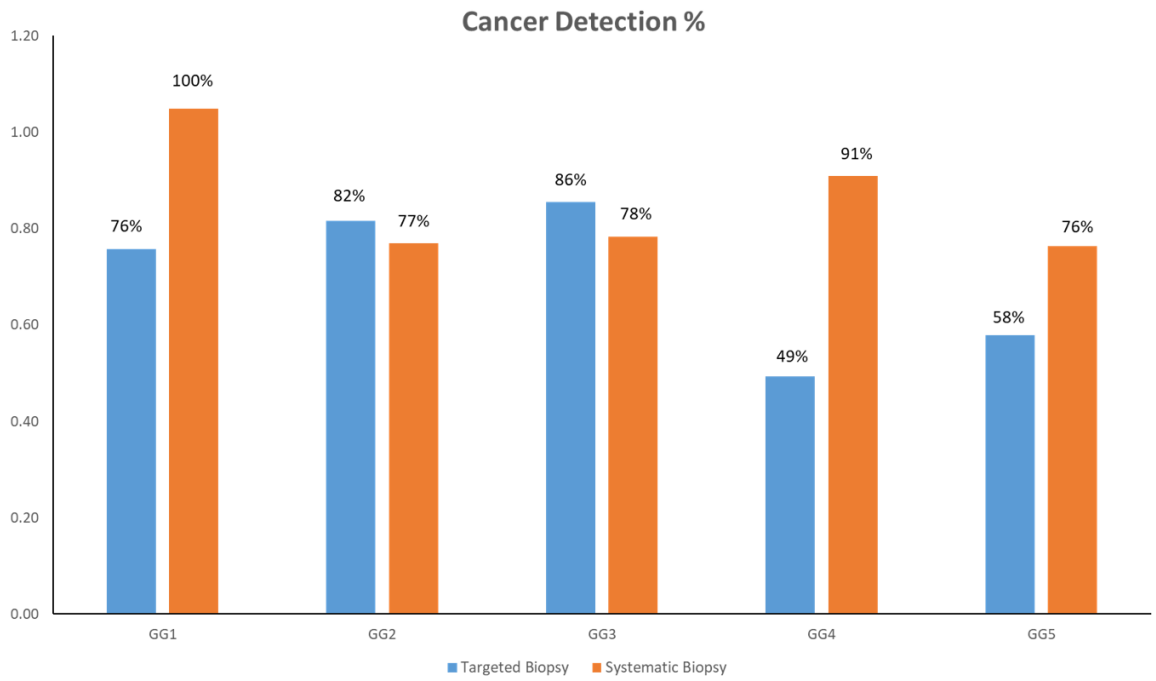

Figure 2. Cancer detection rate in targeted biopsy compared to systematic biopsy in different grade groups (GG).

and 3 cancer cases compared to the systematic biopsy method (82% and 86% as compared to 77% and 78%, respectively; **Figure 2**). However, the systematic biopsy method outperformed the targeted biopsy in the detection of grade group 4 and 5 cancers, with detection rates of 91% and 76% compared to 49% and 58%, respectively (**Figure 2**). We also identified cases in which cancer was detected through the systematic biopsy method, but was missed by the targeted biopsy method. Prostate lesional size, PSA level, and PI-RADS were compared between these two groups using a paired t-tests. In **Figure 3**, we summarize how targeted biopsy was more likely to detect cancer in larger lesions (13.17 mm vs. 11.41 mm, P=0.0056), lesions with associated higher PSA levels (10.38 ng/ml vs. 6.39 ng/ml, P=0.0026), and lesions with higher PI-RADS scales (4.19 vs. 3.68, P<0.0001).

Discussion

Prostate cancer is one of the most common cancers in men worldwide [19]. In the United States, 11% of males are diagnosed with prostate cancer over their lifetime, and the incidence usually rises with age (https://seer.cancer.gov/statfacts/html/prost.html, [20]). Prostate biopsy is an invasive procedure in which tissue samples are obtained from the prostate gland for the purpose of detecting the presence of cancer. A prostate cancer diagnosis may be characterized by a great deal of uncertainty, which can result in both overtreatment and undertreatment [6, 21-23]. Nowadays, with the help of MRI or ultrasound guided biopsy, we are able to diagnose prostate cancer with more certainty [24]. In this study, we evaluated prostate cancer cases with combined targeted biopsy and systematic biopsy to see if there were differences between these two methods for the diagnosis of prostate cancer. We found that the grade group classification was not aligned between the two methods. For example, the systematic biopsy could detect more grade 1 cancer than targeted biopsy. Therefore, the combined method may lead to an increase in cancer detection rates and improve the likelihood that the biopsy findings are predictive of the true pathologic nature of the patient's disease [6]. However, one limitation of our study is that we did not specifically examine the prostatectomy specimen due to its low number of cases. This could have been a good way to grade the overall tumor in order to decide which method is more accurate.

Several earlier studies have concluded that MRI-targeted biopsy overrides systematic biop-

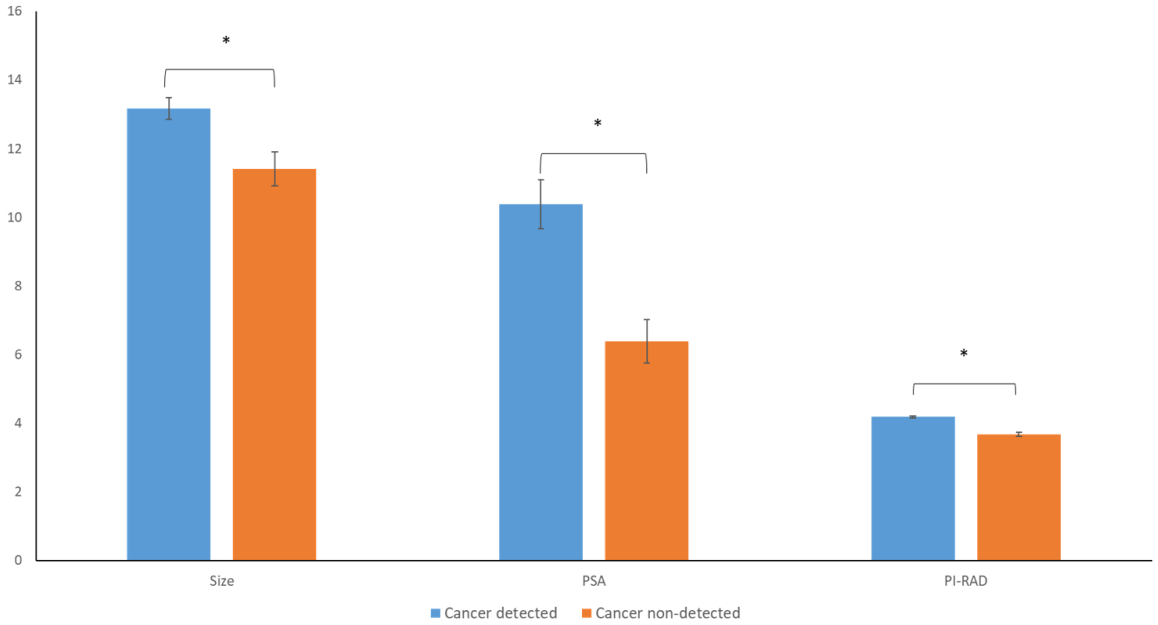

Figure 3. Lesion size, PSA level, and PI-RADS score comparison in target-detected cancer group, and target missed/systematic detected cancer group.

sy in the diagnosis of clinically significant cancer [25-27]. These studies evaluated combined biopsy as a possible improvement in diagnostic methods; however, the investigators did not routinely use MRI-targeted biopsy software or ultrasound-guided scanners, leading to some uncertainty about their conclusions. Our data, which represent a substantially larger population, shows that cancer detection rate rose for both targeted and systematic biopsy under the MRI or ultrasound-targeted biopsy software as the grade group increased. Part of the reason for this may be due to the increased detection rate of the MRI/ultrasound-guided devices, which significantly increased ($P \leq 0.05$) when the cancer was larger, PSA levels were higher, and when PI-RADS scores were higher in our study. Of note, although the overall cancer detection rate rose as the grade group increased, for the grade group 4, the targeted-biopsy detection rate decreased abruptly to 49% (down from 86% of grade group 3) and showed 42% less detection rate than the systematic biopsy group. The reason for this might be that the systematic biopsy is better at detecting higher grade groups since it includes more core biopsy locations [28]. Further investigation is needed.

Our study had a considerable number of patients enrolled. Data collection was continuous and accurate by means of unified diagnosis by experienced pathologists in a large medical institution. These qualifications provide strength to our findings. Targeted biopsy is not sensitive for grade group 1 cancer but is as sensitive as systematic biopsy in detecting higher-grade cancers (i.e., grade group 2 and 3 in our study). However, Gleason scores were significantly lower in the targeted biopsy cores compared to systematic biopsy cores. This might represent the help of imaging in detecting lesions with lower Gleason scores. Also, targeted biopsy is more effective at detecting cancer when the patients have larger lesions, higher PI-RADS scores, and higher PSA levels [18].

Since our study had a retrospective design, imaging studies, biopsies, and morphologic interpretation were carried out by different providers at different times. However, the methodology for each aspect of the diagnosis was uniform. Whether targeted biopsy or systematic biopsy was performed first was not specified by the clinicians, therefore we could not evaluate this consideration in our study. It is possible that one method might use the markers (such as hemorrhage tracks) of the other method to track the lesion and it may affect the results. In that situation, post-biopsy hemorrhage with its hypointensity on T2W and restricted diffusion on MRI could mimic or obscure malignant

lesion(s) [17, 29, 30]. Also, our study did not include the grading of prostatectomy specimens for analysis, as the number of patients who underwent prostatectomy was low. Therefore, we are unable to compare the grade group of gold standard (prostatectomy) with that of systematic biopsy or targeted biopsy. Collectively, the findings of our study suggest that targeted biopsy combined with systematic biopsy improved cancer detection rate compared to systematic biopsy alone. Targeted biopsy does not seem to be sensitive for grade group 1 cancer but is as sensitive as systematic biopsy for detecting higher-grade cancers. In light of our findings, we believe that targeted biopsy technique with MRI/ultrasound enhances the power of cancer detection. However, the application of combined systematic biopsy with targeted biopsy is still not used widely in daily clinical practice. A targeted biopsy requires an experienced urologist and more advanced equipment to perform. In our investigation, if any MRI scans or ultrasound technique were inaccurately categorized as normal or abnormal, such misclassifications could introduce bias. Additionally, given that MRI-targeted biopsies preceded systematic biopsies, it is plausible that MRI-derived data, such as hemorrhage tracks, could have impacted the outcomes of systematic biopsies. Moreover, some invisible lesions were not easily detected by MRI or ultrasound techniques, and urologists could only perform a systematic biopsy if they suspected the patient had an abnormality based on a high PSA level. The choice between these biopsy methods often depends on factors such as patient risk profile, imaging findings, or availability of resources [31, 32].

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Qiusheng Si, Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, Annenberg Building, 1468 Madison Ave, 15, 201, New York, NY 10029, USA. Tel: 212-241-3341; E-mail: qiusheng.si@mountsinai.org

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