Comparison of the diagnostic yield of various systematic randomized prostate biopsy protocols using prostate phantoms made of devil's tongue jelly

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Purpose: The purpose of this study was to compare the diagnostic yield of five systematic randomized protocols using 12–20 biopsy cores with variably-sized phantoms.

Methods: A total of 100 prostate phantom models were produced by casting liquid devil's tongue jelly using silicone molds. Sets of 20 phantoms were created with the following volumes: 20 mL, 40 mL, 60 mL, 80 mL, and 100 mL. Three focal lesions were created by injecting 0.5 mL of warm agar solution stained with red, blue, and green ink into each phantom model. The focal lesions were verified by ultrasonography. The systematic randomized biopsy protocols consisted of 12, 14, 16, 18, and 20 biopsy cores. The diagnostic yield of the multiple systematic biopsy protocols was compared.

Results: The overall detection rates of each model set were 93.3% for 20 mL, 88.3% for 40 mL, 71.7% for 60 mL, 43.3% for 80 mL, and 30.0% for 100 mL. Statistically significant differences in the detection rate were found between 40 mL and 60 mL and between 60 mL and 80 mL. No statistically significant increase in the detection rate was observed within a given volume set even when the number of core biopsies increased from 12 to 20.

Conclusion: The diagnostic yield of systematic randomized biopsies is inversely proportional to the phantom volume.

Keywords: Devil's tongue jelly; Konjac; Prostate; Phantom; Biopsy

Introduction

Since systematic randomized transrectal ultrasound-guided prostate biopsy was introduced in 1989 [1], it has been regarded as the gold standard for the tissue-based diagnosis of prostate cancer. This procedure is easy, safe, and well-tolerated by patients under local anesthesia in an outpatient department. Although prostate biopsy under the guidance of multiparametric magnetic resonance imaging (MRI) is increasingly used in clinical settings, systematic randomized transrectal ultrasound prostate biopsy remains the standard of care for diagnosing patients with clinically suspected prostate

cancer [2,3].

An increase in the number of biopsies has led to improvements in the cancer detection rate [4,5]. However, the number of biopsy cores that can be obtained is usually limited under local anesthesia in clinical settings such as an outpatient office. Increasing the number of biopsies can result in a higher risk of hematochezia and hematospermia in biopsied patients [6]. Moreover, the increase in the number of biopsy cores has led to the identification of more clinically insignificant cancers [7], resulting in overtreatment. The detection of clinically significant cancer, which determines a patient's prognosis, is an important strategy in prostate cancer management.

Ideally, the number of prostate biopsy cores should maximize the detection of clinically significant cancer, while not increasing the detection of clinically insignificant cancer. Prostate volume is another important factor to consider in determining the number of biopsy cores. The detection rate of cancer is inversely proportional to the prostate volume. Ploussard et al. [8] reported that the number of biopsy cores should be increased in patients with a larger prostate in order to maintain diagnostic sensitivity. However, the optimal number of biopsy cores corresponding to specific prostate volumes has not yet been determined.

The present study aimed to compare the diagnostic yield of five systematic randomized protocols, ranging from 12 biopsy cores to 20 biopsy cores, in variably-sized prostate phantoms with a simulated clinically significant prostate cancer core.

Materials and Methods

Phantom Production

This study used devil's tongue jelly as a prostate model that showed echoes similar to the prostate gland, was easy to handle, and enabled the creation of focal lesions. First, we created initial prostate patterns using devil's tongue jelly. To do so, 10 g of powdered jelly (HoiKonjac, Miryang Agar-Agar, Miryang, Korea) was dissolved in 200 mL of boiling distilled water. The solution was stirred to avoid making bubbles. The solution was apportioned using 20 mL, 40 mL, 60 mL, 80 mL, and 100 mL syringes. The solution was then inserted into latex balloons and cooled at room temperature. We created five prostate patterns with different volumes. Second, we made a silicone mold to pour liquid silicone into the jelly patterns. Finally, the liquefied solution of jelly was poured into each hole in the silicone mold to produce the prostate phantom models (Fig. 1). The volume of each final phantom model was measured by immersion using Archimedes' principle. Each volume set consisted of 20 phantoms, producing a total of 100 phantoms with fvie different volumes.

We injected 0.5 mL of warm agar solution stained with red, blue,

Fig. 2. A prostate phantom with three focal lesions. A total of 0.5 mL of warm agar solutions stained with red, blue, and green ink was injected using a 1 mL syringe to simulate a focal lesion in the prostate phantom. Each lesion is located at base, midgland and apex of the prostate phantom.
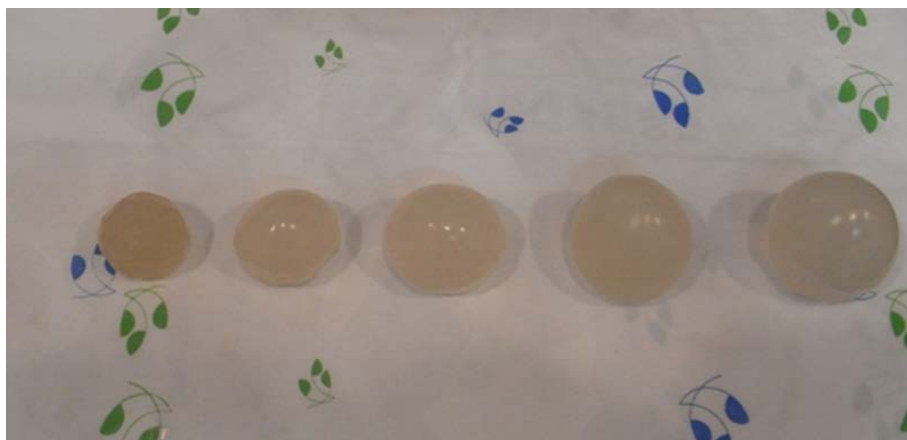

Fig. 1. Variable-sized prostate phantoms. Prostate phantoms of 20, 40, 60, 80, and 100 mL were made from devil's tongue jelly, produced by pouring the liquefied solution of jelly in the silicone mold.
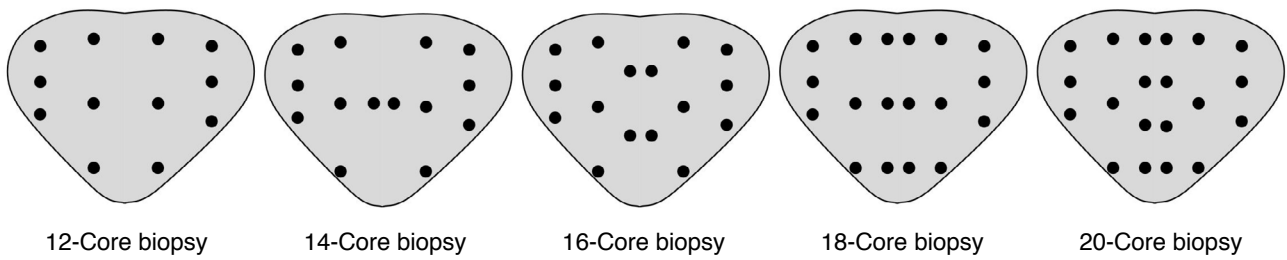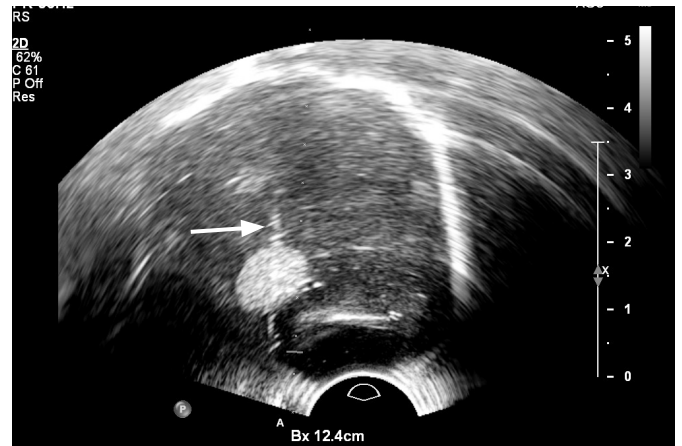
Fig. 3. **Variable biopsy schemes.** Five different biopsy schemes, ranging from 12 to 20 cores, were used for the biopsies.

A

B

Fig. 4. **Randomized biopsy of a prostate phantom.**
A. While research assistant manually held the phantom covered with black plastic envelope, biopsies were done by a uroradiologist. B. Ultrasonographic scan during biopsy shows focal hyperechoic nodule made from agar solution and biopsy trajectory hitting the focal lesion is seen (arrow).

and green ink using a 1-mL syringe to simulate a focal lesion in the prostate (Fig. 2). Three focal lesions were made in each prostate phantom. Gaps at intervals of at least 1 cm were created between the stained agar areas to avoid overlapping during injection. All the injected focal lesions were verified using an iU22 ultrasound scanner (Philips, Bothell, WA, USA) equipped with a 9–4 MHz broadband curved array endocavitary transducer.

Biopsy and Confirmation

After creating the phantoms, we covered them with black plastic envelopes to cover the transparent phantoms with focal lesions, thereby mimicking a systematic randomized biopsy. Five different biopsy protocols were applied, with 12, 14, 16, 18, and 20 biopsy cores, respectively. For each biopsy protocol, the biopsy was performed in the corresponding sectors according to the scheme shown in Fig. 3, while a research assistant manually held the phantom (Fig. 4A, B). All the biopsies were done by a single uroradiologist with 14 years of experience conducting

prostate biopsies. Each volume set with 20 phantoms contained four phantoms in which the same biopsy protocol was used. An 18-gauge, 15-cm automatic cutting needle and an automated biopsy gun (ACECUT, TSK Laboratory, Tochigi, Japan) were used. We confirmed the presence of ink in the biopsy specimen core with a stereomicroscope (SZ2-ILST, Olympus, Tokyo, Japan).

Statistical Analysis

The mean, standard deviation, and coefficient of variance of the phantoms were calculated to ensure that they had the correct volume. The mean diameter of the focal lesion was measured. The detection rates were compared among the different phantom volumes and the different biopsy protocols. The detection rates among the different biopsy protocols in a given volume set were compared using the chi-square test. The number of biopsy cores per lesion among each volume set was compared using the independent t test. All statistical analyses were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

Results

Validation of the Prostate Phantoms and Focal Lesions

Table 1 shows the distribution of the volumes of the produced prostate phantoms. The volumes of the phantoms deviated from the standard patterns by less than 10%. The coefficient of variation or standard deviation that exceeded the average ranged from 0.02 to 0.05. The mean diameter of the focal lesions was 10.1±1.5 mm.

Comparison of Detection Rates and the Number of Positive Biopsy Cores per Lesion

The overall detection rates of the focal lesions in the phantom volumes of 20 mL, 40 mL, 60 mL, 80 mL, and 100 mL were 93.3% (56 of 60), 88.3% (53 of 60), 71.7% (43 of 60), 43.3% (26 of 60), and 30.0% (18 of 60), respectively, for all biopsy protocols. The detection rate of the focal lesions was inversely correlated with the phantom volume. However, statistically significant differences in the detection rate were only seen between phantom volumes of 40 mL and 60 mL and between phantom volumes of 60 mL and 80 mL (Fig. 5). No significant differences were found in the overall detection rate of the focal lesions using the different biopsy protocols (Fig. 6).

No statistically significant differences in the detection rate were observed within a given volume set, even as the number of biopsy cores increased (Fig. 7). The mean number of positive biopsy cores per lesion was statistically significantly different among all the volume sets (Table 2).

Table 1. Average, SD, and coefficient of variation in the sets (n=20) of prostate phantoms with different volumes

	Prostate phantom				
	20 mL	40 mL	60 mL	80 mL	100 mL
Average (mL)	20.93	40.90	60.38	81.67	100.70
SD	1.07	1.33	1.12	3.62	2.67
Coefficient of variation	0.051	0.032	0.019	0.044	0.027

SD, standard deviation.

Table 2. Average and SD of the number of positive cores per lesion in the sets (n=60) of prostate phantoms with different volumes

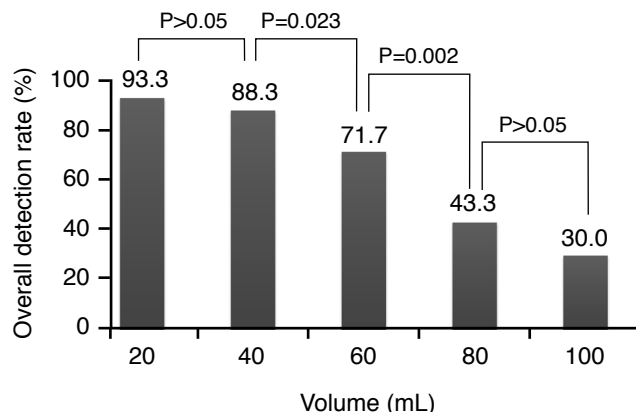|	No. of positive cores per lesion				
	20 mL	40 mL	60 mL	80 mL	100 mL
Average	2.17	1.53	1.10	0.65	0.35
SD	1.20	1.08	0.95	0.94	0.58
P-value[a]		<0.05	<0.05	<0.05	<0.05

SD, standard deviation.

[a]Independent t test.

Fig. 5. Overall detection rates of the focal lesions by phantom volume. There was no statistically significant difference between the 20 mL and 40 mL phantom volumes. However, statistically significant differences in the overall detection rates were found between the 40 mL and 60 mL and the 60 mL and 80 mL volumes.
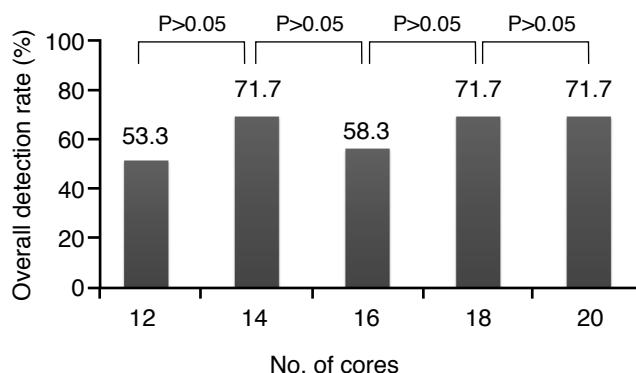

Fig. 6. Overall detection rates of the focal lesions based on biopsy schemes. There was no statistically significant difference in the overall detection rates for the biopsy schemes in these models.
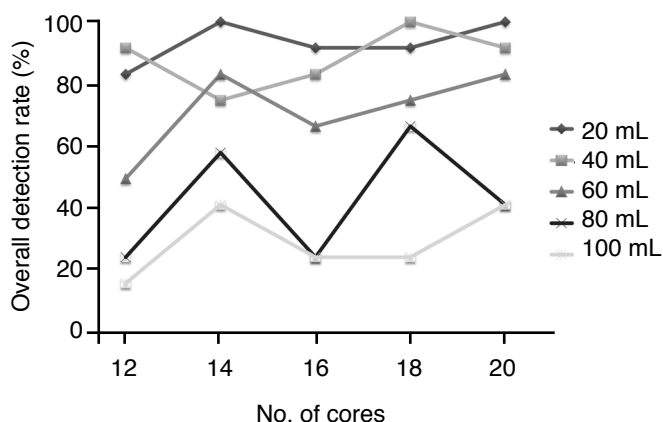

Fig. 7. Detection rates of the focal lesions within the subgroups of the same volume based on biopsy schemes. No statistically significant differences in the detection rates were observed within a given volume set.

Discussion

Prostate phantom volume had the greatest impact on the detection rate of focal lesions in this study. If the phantom volume exceeded 80 mL, even the extended systematic biopsy scheme with 20 cores showed a detection rate of less than 50%. However, a detection rate of greater than 80% was seen in the phantoms with a volume less than 40 mL with 12 core biopsies. The increase in the number of biopsy cores did not result in a statistically significant difference in these phantoms. This finding may counteract the perceived need to further increase the number of prostate biopsy cores in patients with relatively small prostate volumes in a clinical setting.

We made three 0.5-mL focal lesions in each phantom, creating a 1.5-mL tumor in each prostate volume set. Therefore, the tumor volume percent in each phantom set was 7.5%, 3.8%, 1.9%, 0.9%, and 0.5%, respectively. Although we created three lesions in each phantom, the detection rates were only evaluated by lesion based, because the increased number of focal lesions was mainly used to augment the detection rate. In a clinical setting, an increase in the number of biopsies is associated with an increase in the detection rate, especially if the prostate volume is greater than 55 mL [9]. This difference between our study and biopsies performed in a clinical setting could be attributed to the fact that the tumor volume percent in a clinical setting is usually larger than what was used in our phantom study models.

Cho et al. [10] used devil's tongue jelly to make prostate phantoms to evaluate ultrasound-guided targeted biopsies. They created a prostate model by cutting the surface of a jelly ball and varying the volume, ranging from 30 to 40 mL. The created volume was relatively within narrow range and inconsistent. We solved the problem of a limited and imprecise volume range by using a silicone mold. The silicone mold made from the initial jelly patterns with exact volumes (Fig. 1) enabled us to easily and rapidly make a prostate phantom with a reliable volume. Although focal lesions made using agar are easily visualized on ultrasonography (US), we did not plan to target the biopsy using US guidance. The main purpose of the study was to evaluate systematic randomized biopsy protocols according to prostate phantom volume. Moreover, in actual clinical settings, only 11%–35% of tumors are visible on US, and only 17%–57% of US-detected hypoechoic lesions are malignant [11]. This means that targeting tumors using US only plays a minor role in the tissue-based diagnosis of prostate cancer.

Recently, the use of multiparametric MRI and magnetic resonance (MR)–guided biopsy for prostate biopsies has been gaining ground. In 2017, the American Urologic Association policy statements recommended the use of MRI in patients with a previous negative biopsy and ongoing concerns about an increased risk of prostate cancer [2]. However, in biopsy-naïve patients, a systematic randomized prostate biopsy remains the standard approach. The American College of Radiology also maintains a similar policy; consequently, US-guided randomized biopsy remains the standard of care for diagnosis in patients with clinically suspected prostate cancer [3]. Based on our results, the cancer detection rate using systematic randomized biopsy may be lower in patients with a larger prostate. If a patient is at low risk, with a low serum prostate-specific antigen level, the detection rate will be lower. MRI-guided biopsy may be more effective in this case. Walton Diaz et al. [12] reported that MR-US fusion targeted biopsy is a promising solution for patients with a larger prostate in whom prostate cancer is suspected. Bey et al. [13] likewise reported that younger patients with a larger prostate and a prior negative biopsy were more likely to be offered an MR-US fusion biopsy.

The present study has some limitations. First, we created a 0.5-mL focal lesion according to Epstein's criteria for clinically significant cancer [14]. If the lesion volume is less than 0.5 mL, cancer with a Gleason score over 7 is still regarded as clinically significant. However, we only focused on targeting cancer with a systematic randomized biopsy using Epstein's size criteria. Second, no detailed anatomical information was included in our phantom study. We tried to make each lesion at the base, mid-gland, and apex of the phantoms during the injection of colored agar solution to mimic the multifocality of prostate cancer. Therefore, all focal lesions in a prostate do not have the same chance of being biopsied.

In conclusion, phantom volume is a major factor determining the detection rate of focal lesions. We suggest that a systematic randomized biopsy of 12 cores may be sufficient for the detection of clinically significant prostate cancer if the volume of the prostate is less than 40 mL. If the volume of the prostate is around 60 mL, the 14-core protocol showed a comparably high detection rate of cancer. However, if the volume of the prostate is over 80 mL, simply increasing the number of biopsy cores is not sufficient for diagnosing clinically significant cancer with relatively small lesions. MR-guided or targeted biopsy would be more beneficial in patients with prostates of this size or larger.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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