How Many Cores Does Systematic Prostate Biopsy Need?

A Large-Sample Retrospective Analysis

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Objectives—To explore the best individualized systematic prostate biopsy method.

Methods—We retrospectively analyzed the clinical data of 1211 patients who underwent 12-core systematic prostate biopsy guided by transrectal ultrasound from January 2011 to March 2018. Other biopsy core methods (6-, 8-, and 10-core) were estimated from the 12-core biopsy that was performed. Differences in the detection rates of prostate cancer (PCa) and clinically significant prostate cancer (csPCa) were compared.

Results—A total of 498 cases of PCa (41.1%) were detected, and 423 cases (34.9%) were csPCa. There was no significant difference between the 12- and 10-core prostate biopsy strategies in the total detection rates of PCa and csPCa ($P > .05$). In the subgroup of patients with a maximal prostate cross-sectional area of less than 15 cm^2, there was a significant difference between the 12-core method and the standard 6-core method ($P = .03$) but no significant differences between the other methods in the detection rate of PCa ($P > .05$), but in the detection rate of csPCa, the 12-core method differed significantly from the other methods (P = .02–.04) except for the 10-core method ($P > .05$). In patients with a prostate-specific antigen concentration of 20 ng/mL or higher, there were no significant differences between the 12-core method and all of the other methods ($P > 0.05$). In patients younger than 70 years and 70 years or older, the 12-core method differed significantly from the other methods ($P < .01$–$.03$) except for the 10-core method ($P > .05$).

Conclusions—Ten- or 12-core biopsy showed a higher detection rate than the other schemes. However, for patients with a prostate-specific antigen concentration of 20 ng/mL or higher, the 6-core systematic biopsy is preferred.

Key Words—biopsy; prostatic neoplasm; transrectal; ultrasound

With the progress of medical technology and the improvement of people's quality of life, the average life expectancy of humans has been prolonged. However, the prevalence of prostate cancer (PCa) is also increasing in the population.[1] In Europe, there are approximately 350,000 new cases of PCa each year. In the United States, approximately 210,000 new cases are reported each year, accounting for approximately one-fourth of all new malignancies in men. The incidence rate of PCa ranks the highest among all male malignancies, and the mortality rate ranks second only after lung cancer in some countries.[2] The PCa prevalence in China is low, ranking eighth among male malignancies, but its prevalence has increased over the years. According to a survey in 2013, the prevalence of PCa in China showed a yearly increase of 12.07% from 1990 to 2013.[3,4]

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Abbreviations

csPCa, clinically significant prostate cancer; PCa, prostate cancer; PSA, prostate-specific antigen; US, ultrasound

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Prostate cancer screening methods include serum prostate-specific antigen (PSA) testing, digital rectal examinations, and ultrasound (US) examinations, but the sensitivity and specificity of these methods for the diagnosis of PCa are low and cannot meet the clinical requirements for the diagnosis of PCa. Magnetic resonance imaging has good spatial resolution and good contrast resolution for soft tissues and is the best preoperative imaging examination method for PCa.[5,6] However, the preoperative pathologic diagnosis still relies on biopsy.

Hodge et al[7] proposed transrectal US-guided 6-core systematic biopsy, which is a milestone in the diagnosis of PCa and is gradually becoming the reference standard for preoperative PCa diagnosis. However, with the deepening of research in this field, it has been found that this method still leads to an approximately 33% misdiagnosis rate for PCa.[8] To improve the detection rate for PCa, modified 6-, 8-, 10-, 12-, and 13-core and even saturation biopsies have been developed on the basis of the 6-core systematic biopsy.[9,10] Increased numbers of biopsy cores can improve the detection rate of PCa. It has been confirmed that the 12-core systematic and saturation biopsy strategies can lead PCa detection rates of 30% to 50%, but these strategies also detect more cases of PCa without clinical significance[11] and increase the risk of bleeding, infection, erectile dysfunction, and other complications.[12] Studies have also shown that when the number of biopsy cores reaches a certain level, subsequent increases in the number of biopsy cores cannot further improve the detection rate of PCa.[13] A reasonable biopsy strategy should minimize the patient's trauma and reduce pain while achieving optimal diagnostic efficiency. Therefore, for patients receiving their first biopsy, choosing a reasonable biopsy strategy is still a difficult problem faced by clinicians. In this study, we conducted a large-sample retrospective analysis and explored personalized transrectal US-guided prostate biopsy strategies.

Materials and Methods

Participants

This study retrospectively analyzed patients who underwent 12-core transrectal US-guided prostate biopsy for suspected PCa at Peking University Third Hospital and Peking University Shenzhen Hospital from January 2011 to March 2018. The study was approved by the Institutional Review Board of Peking University Third Hospital and Peking University Shenzhen Hospital. Written informed consent was obtained from each patient before prostate biopsy.

The inclusion criteria were as follows: (1) cases with nodules detected on a digital rectal examination with any PSA value; (2) cases with abnormal nodules revealed on an imaging examination with any PSA value; (3) cases with a PSA concentration of greater than 10.0 ng/mL and any free PSA/total PSA value; and (4) cases with a PSA concentration of 4.0 to 10.0 ng/mL and a free PSA/total PSA value of less than 0.18. The exclusion criteria were as follows: (1) cases with previous biopsy; (2) cases unable to complete the 12-core biopsy; (3) cases with antiandrogen therapy; and (4) cases with incomplete data.

A total of 1211 patients were enrolled. According to serum PSA concentrations, patients were divided into a group with PSA concentrations of 20 ng/mL or higher and a group with PSA concentrations of less than 20 ng/mL. According to the maximal prostate cross-sectional area, patients were divided into a group with cross-sectional areas of 15 cm^2 or greater and a group with cross-sectional areas of less than 15 cm^2. According to age, patients were divided into a group that was younger than 70 years and a group that was 70 years or older. The differences in PCa detection rates were analyzed among biopsy methods with different core numbers in different groups.

Instruments and Equipment

We used a ProSound α10 color Doppler US system (Aloka Co, Ltd, Tokyo, Japan) equipped with an end-launched transrectal transducer with a frequency of 5 to 9 MHz and a special metal guide frame. We also used a Bard automatic biopsy gun and an 18-gauge biopsy needle (C. R. Bard, Covington, GA).

Prostate Biopsy Method

Routine preoperative blood examinations were conducted, and coagulation functions and serum PSA concentrations were measured. If patients used aspirin, warfarin, and other anticoagulants, they were requested to stop using the drugs for 1 week. On the day of the procedure, patients began to take quinolone antibiotics (levofloxacin). Patients also

Figure 1. Biopsy point distribution diagram for the 12-core method.

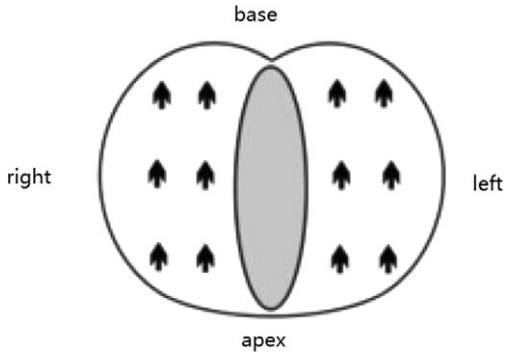


Figure 2. Biopsy point distribution diagram for the 6-core method (6 points inside the red rectangles).

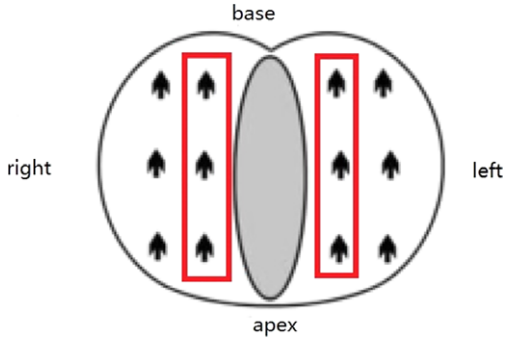


Figure 3. Biopsy point distribution diagram for the modified 6-core method (6 points inside the red rectangles).

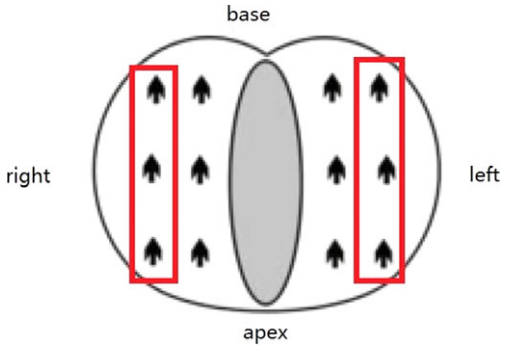
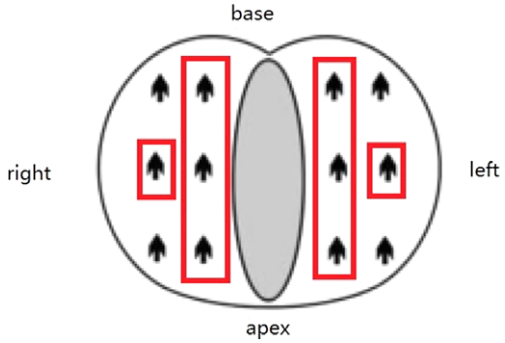


Figure 4. Biopsy point distribution diagram for the 8-core method (8 points inside the red rectangles).



underwent a cleansing enema on the day of biopsy and continued taking antibiotics for a total of 3 days after the procedure.

Patients were in the left knee flexion position, and the perianal area and lower rectum were disinfected with 0.5% iodophor. The biopsy process was conducted without anesthesia. The rectal transducer was placed, and the maximal prostate cross-sectional area was routinely measured. All patients underwent 12-core systematic biopsy, and the biopsy points were distributed symmetrically at the base, mid gland, and apex of the prostate according to the traditional systematic biopsy method (Figure 1).

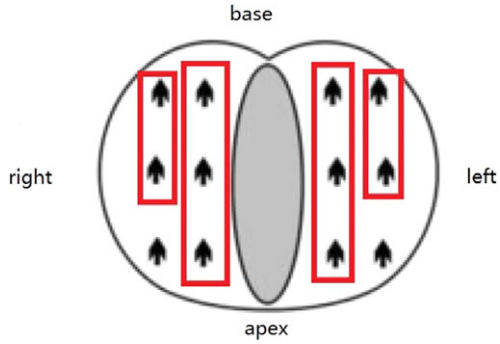
The other biopsy cores were only estimated from the 12-core biopsy that was performed. The standard 6-core biopsy method uses the medial points at the base, mid gland, and apex of the prostate (Figure 2); the modified 6-core biopsy method uses the lateral points at the base, mid gland, and apex of the prostate (Figure 3); the 8-core method uses the sites of the standard 6-core biopsy method plus the bilateral points at the mid gland (Figure 4); and the 10-point method uses the points of the standard 6-core method plus the bilateral points at the base and the mid gland (Figure 5).

After biopsy, an iodophor-soaked cotton ball was pressed to the local rectal area to achieve hemostasis in patients with substantial bleeding. Patients were required to drink more water and urinate often. Tissues from different biopsy sites were placed separately in specimen bottles, and each bottle was labeled with the corresponding anatomic position. The tissues in the bottles were then fixed with 10% formalin.

Calculation of the Maximal Prostate Cross-sectional Area

Because this study was a retrospective analysis, the information used was the historical data retrieved

Figure 5. Biopsy point distribution diagram for the 10-core method (10 points inside the red rectangles).



from the picture archiving and communication system. In our hospital, we only saved the maximal cross-sectional area images of the prostate and biopsy guide map for prostate biopsy and did not save the longitudinal prostate images. Therefore, it was not possible to calculate the prostate volume, so the maximal prostate cross-sectional area was used instead. The calculation method was based on the calculation of the elliptical area as follows: area = $\pi \times A \times B/4$, where A is the small prostate diameter, and B is the large diameter perpendicular to the small diameter.

Definition of Clinically Significant Prostate Cancer

According to Ahmed et al,[14] we defined clinically significant prostate cancer (csPCa) as a Gleason score of 7 or higher in any biopsy core or and Gleason score of 6 or lower with a tumor length of greater than 4 mm.

Statistical Analysis

We used SPSS version 17.0 statistical software (IBM Corporation, Armonk, NY) to analyze the results. The measurement data were expressed as mean ± standard deviation. The means of different groups were compared by an independent-sample t test. The PCa detection rates for the different biopsy methods were compared by the χ^2 test, and $P < .05$ indicated that the difference was statistically significant.

Results

A total of 1211 cases were enrolled. The patients were aged 41 to 86 years, with a mean of 67.85 ± 9.07 years. The serum PSA concentrations were 0.44 to 528 ng/mL, with a mean of 15.10 ± 12.06 ng/mL. The maximal cross-sectional areas of the prostate were 10.8 to 33.5 cm^2, with a mean of 16.6 ± 6.3 cm^2.

Table 1. Prostate Cancer Detection Rates for Different Biopsy Strategies

Method	Benign	Malignant	χ^2	*P*
12-core	713	498		
10-core	759	452	3.67	.056
8-core	789	422	10.12	< .01
Modified 6-core	793	418	11.24	< .01
Standard 6-core	818	393	19.58	< .01

Statistical values were derived from comparisons with the 12-core method.

The total PCa detection rate was 41.1% (498 of 1211), and the csPCa detection rate was 34.9% (423 of 1211). The differences in PCa and csPCa detection rates between prostate biopsy methods with different numbers of cores are listed in Tables 1 and 2. The 12-core biopsy strategy did not differ significantly from the 10-core biopsy method but did differ significantly from the 8-, modified 6-, and standard 6-core methods.

The impacts of different biopsy strategies on PCa and csPCa detection rates in the groups based on the maximal prostate cross-sectional areas are shown in Tables 3 and 4. When the maximal cross-sectional area was less than 15 cm^2, there were no significant differences in the detection rates of PCa between the 10-, 8-, and modified 6-core biopsies and the 12-core method. When the maximal cross-sectional area was 15 cm^2 or greater, there were significant differences in the detection rates of PCa between the 12-core method and all of the other methods. For the detection of csPCa, the 12-core biopsy strategy did not differ significantly from the 10-core biopsy method but did differ significantly from the 8-, modified 6-, and standard 6-core methods.

The impacts of different biopsy strategies on PCa and csPCa detection rates according to different serum PSA concentrations are shown in Tables 5 and 6. When the PSA concentration was 20 ng/mL or higher, there were no statistically significant differences in the detection rates of PCa and csPCa between the 12-core method and any of the other methods. When the PSA concentration was lower

Table 2. Clinically Significant PCa Detection Rates for Different Biopsy Strategies

Method	Benign and Non-csPCa	csPCa	χ^2	*P*
12-core	788	423		
10-core	832	379	3.61	.057
8-core	856	355	8.76	< .01
Modified 6-core	860	351	9.84	< .01
Standard 6-core	866	345	11.60	< .01

Statistical values were derived from comparisons with the 12-core method.

Table 3. Prostate Cancer Detection Rates for Different Biopsy Strategies in Groups With Different Maximal Prostate Cross-sectional Areas

	Cross-sectional Area < 15 cm^2				Cross-sectional Area ≥ 15 cm^2			
Method	Benign	Malignant	χ^2	*P*	Benign	Malignant	χ^2	*P*
12-core	213	152			500	346		
10-core	219	146	0.204	.65	540	306	3.992	.04
8-core	231	134	1.863	.17	558	288	8.486	<.01
Modified 6-core	233	132	2.305	.13	560	286	9.092	<.01
Standard 6-core	242	123	4.907	.03	576	270	14.745	<.01

Statistical values were derived from comparisons with the 12-core method.

Table 4. Clinically Significant PCa Detection Rates for Different Biopsy Strategies in Groups With Different Maximal Prostate Cross-sectional Areas

	Cross-sectional Area < 15 cm^2				Cross-sectional Area ≥ 15 cm^2			
Method	Benign and Non-csPCa	csPCa	χ^2	*P*	Benign and Non-csPCa	csPCa	χ^2	*P*
12-core	231	134			557	289		
10-core	247	118	1.55	.21	585	261	2.11	.15
8-core	257	108	4.18	.04	599	247	4.82	.03
Modified 6-core	258	107	4.52	.03	602	244	5.55	.02
Standard 6-core	260	105	5.23	.02	606	240	6.60	.01

Statistical values were derived from comparisons with the 12-core method.

Table 5. Prostate Cancer Detection Rates for Different Biopsy Strategies in Groups With Different Serum PSA Concentrations

	PSA < 20 ng/mL				PSA ≥ 20 ng/mL			
Method	Benign	Malignant	χ^2	*P*	Benign	Malignant	χ^2	*P*
12-core	633	324			67	162		
10-core	674	283	4.056	.04	69	160	0.224	.64
8-core	697	260	8.139	<.01	72	157	1.266	.26
Modified 6-core	699	258	10.755	<.01	74	155	1.713	.19
Standard 6-core	721	236	19.548	<.01	79	150	2.506	.11

Statistical values were derived from comparisons with the 12-core method.

than 20 ng/mL, the differences in the detection rates of PCa between the 12-core method and all of the other methods were statistically significant. For csPCa, the 12-core biopsy strategy did not differ significantly from the 10-core biopsy method but did differ significantly from the 8-, modified 6-, and standard 6-core methods.

The impacts of different biopsy strategies on PCa and csPCa detection rates according to different ages are shown in Tables 7 and 8. The 12-core biopsy method did not differ significantly from the 10-core

Table 6. Clinically Significant PCa Detection Rates for Different Biopsy Strategies in Groups With Different Serum PSA Concentrations

	PSA < 20 ng/mL				PSA ≥ 20 ng/mL			
Method	**Benign and Non-csPCa**	**csPCa**	χ^2	***P***	**Benign and Non-csPCa**	**csPCa**	χ^2	***P***
12-core	677	280			111	143		
10-core	705	252	2.04	.15	127	127	2.02	.16
8-core	728	229	6.96	.01	128	126	2.28	.13
Modified 6-core	732	225	8.14	<.01	128	126	2.28	.13
Standard 6-core	736	221	9.41	<.01	130	124	2.85	.09

Statistical values were derived from comparisons with the 12-core method.

Table 7. Prostate Cancer Detection Rates for Different Biopsy Strategies in Groups With Different Ages

	Age < 70 y				Age ≥ 70 y			
Method	**Benign**	**Malignant**	χ^2	***P***	**Benign**	**Malignant**	χ^2	***P***
12-core	294	203			419	295		
10-core	318	179	2.449	.12	441	273	1.415	.23
8-core	329	168	5.268	.02	460	254	4.974	.03
Modified 6-core	332	165	6.231	.01	461	253	5.224	.02
Standard 6-core	341	156	9.632	<.01	477	237	10.078	<.01

Statistical values were derived from comparisons with the 12-core method.

Table 8. Clinically Significant PCa Detection Rates for Different Biopsy Strategies in Groups With Different Ages

	Age < 70 y				Age ≥ 70 y			
Method	**Benign and Non-csPCa**	**csPCa**	χ^2	***P***	**Benign and Non-csPCa**	**csPCa**	χ^2	***P***
12-core	324	173			464	250		
10-core	343	154	1.65	.20	489	225	1.97	.16
8-core	354	143	4.18	.04	502	212	4.62	.03
Modified 6-core	356	141	4.77	.03	504	210	5.13	.02
Standard 6-core	359	138	5.73	.02	507	207	5.98	.02

Statistical values were derived from comparisons with the 12-core method.

method for the PCa and csPCa detection rates but was statistically different from the 8-, modified 6-, and standard 6-core methods.

Discussion

Systematic prostate biopsy is the reference standard for preoperative diagnosis of PCa. Since Hodge et al[7] started to apply the standard 6-core systematic biopsy at the end of the 1980s, this method has been widely used, followed by the rapid development of different biopsy methods, such as the modified 6-, 8-, and 12-core and saturation methods.[10]

Because the sensitivity and specificity of transrectal US in the diagnosis of PCa are low, systematic biopsy is based on anatomic division of the prostate. For the standard 6-core biopsy, the biopsy sites are located in the prostate lateral lines; the biopsy area contains parts of the peripheral and central zones, and PCa mainly occurs in the peripheral zone. Current studies show that the false-negative rate for the standard 6-core method can range from 20% to 40%.[10,15–17] The 13-core, 5-zone biopsy substantially increases the incidence of complications such as hematuria without an appreciable increase in the PCa detection rate because this method obtains 3 cores in the central area.[18] There is no consensus on the

choice of 8-, 10-, and 12-core biopsy methods, with different scholars reaching different conclusions. In theory, increasing the number of biopsy sites, especially the number of peripheral biopsy sites, can increase the detection rate of PCa, while also increasing the incidence rates of patient discomfort and complications. Xu et al[19] compared the positive detection rates and complications of the 6-, 10-, 12-, and 14-core biopsy methods and concluded that the 10-core method was the most suitable method for prostate biopsy, and further increasing the number of biopsy cores did not significantly improve the positive detection rate. Research has shown that complications can be substantially increased when the number of biopsy cores exceeds 12.[20–22] Therefore, balancing between detection and complication occurrence rates is a dilemma for urologists.

This study showed that there was no statistically significant difference between the 12- and 10-core biopsy methods in the overall PCa and csPCa detection rates, but a careful analysis revealed that the *P* values were .056 and .057, approaching the critical value. In addition, the PCa and csPCa detection rates for the 12-core method were 41.1% and 34.9%, respectively, whereas the rates for the 10-core biopsy method were 37.3% and 31.3%, indicating that the application of the 10-core biopsy method could lead to misdiagnosis rates of approximately 9% in patients with PCa and 10% in those with csPCa. Therefore, we believe that application of the 12-core biopsy method is reasonable for patients receiving biopsy for the first time. Yamaguchi et al[23] used the 13-core biopsy method and showed that there was no statistically significant difference in the positive detection rates between the 13- and 10-core methods after excluding the 3 central cores. The main reason for this lack of a difference is that the central 3 cores included in the biopsy method are located in the central area, which has a low incidence of PCa, and these cores do not have substantial roles in PCa detection. In this study, the 12 biopsy sites were mainly distributed in the peripheral zone of the prostate, which has a high incidence of PCa; therefore, increasing the number of biopsies in the peripheral zone of the prostate is more conducive to improving the detection rate of PCa.

The results of this study show that the detection rate of the 8-core method was similar to that of the modified 6-core method; the difference between them was not statistically significant, and both methods are superior to the standard 6-core method, consistent with the view of Ukimura et al.[24] The biopsy sites of the modified 6-core method lean toward the far lateral area, and the biopsy path crosses many tissues in the peripheral zone, whereas the biopsy sites of the standard 6-core method are located in the prostate lateral line, and the biopsy path includes both the peripheral and central zones. In patients with benign prostatic hyperplasia, a substantial increase in the volume of the central zone, which compresses the peripheral zone, results in considerable thinning of the peripheral zone. Therefore, a biopsy of this region will sample substantially fewer tissues of the peripheral zone and will reduce the detection rate of PCa. The results show that an increased number of biopsy sites in the peripheral zone of the prostate can significantly improve the detection rate of PCa and can reduce misdiagnosis.

A comparison of groups based on different maximal prostate cross-sectional areas showed that the 12-core method did not differ significantly from the 10-, 8-, and modified 6-core methods in the detection rate of PCa in patients with an area of less than 15 cm^2 but was significantly different from the standard 6-core method. In patients with areas of 15 cm^2 or greater, the 12-core method showed statistically significant differences in the detection rates compared with all of the other methods. For the detection of csPCa, the 12-core biopsy strategy did not differ significantly from the 10-core biopsy method but did differ significantly from the 8-, modified 6-, and standard 6-core methods. In a previous study, Porcaro et al[25] suggested that for smaller prostates, a relatively small number of biopsy cores can lead to a satisfactory detection rate, whereas for larger prostates, the number of biopsy cores needs to be increased.

In this study, we compared the results between groups with different serum PSA concentrations. In patients with a PSA concentration of 20 ng/mL or higher, there were no significant differences in the PCa and csPCa detection rates for the different biopsy methods. Therefore, to reduce trauma to patients, a 6-core biopsy is sufficient to diagnose PCa in patients with a PSA concentration of 20 ng/mL or higher. Although the differences between the standard 6-core, modified 6-core, and 12-core methods

were not statistically significant, the modified 6-core method had a slightly higher detection rate than the standard 6-core method; therefore, the modified 6-core method is recommended. For patients with a PSA concentration of less than 20 ng/mL, the 12-core biopsy method was superior to the other methods. The positive biopsy rate is high in patients with a PSA concentration of 20 ng/mL or higher, and the cancerous lesions are more extensively distributed in these patients and are easily detected via biopsy. Therefore, only a few biopsy cores are sufficient to reach a diagnosis. In contrast, for patients with a PSA concentration of less than 20 ng/mL, the tumors are mostly focal, and increased numbers of biopsy sites are conducive to tumor detection.[26]

Results of the age grouping showed that there were no statistically significant differences between the 12- and 10-core biopsy methods for both the group that was 70 years and older and the group that was younger than 70 years, whereas the 12-core biopsy method differed significantly from any of the other biopsy methods in the PCa and csPCa detection rates. This finding shows that grouping based on different ages does not affect the choice of the prostate biopsy method.

Since this study was a retrospective analysis, it was subject to data collection restrictions and did not provide information about postoperative complications. However, current studies have shown that the incidence rates of complications did not differ significantly among the 8- to 12-core biopsy methods.[20,27] Therefore, we believe that if there is evidence supporting statistically significant differences in the PCa and csPCa detection rates, we should use the biopsy method with the higher detection rate. This work was a retrospective study, and all of the information used was based on historical data from a US workstation. Since the US workstation does not retain longitudinal prostate images, the prostate volume could be calculated. Using only the maximal prostate cross-sectional area to represent the prostate size might have affected the results. Another shortcoming of this study was that we used the 12-core biopsy as the final reference standard, and studies have shown that compared with radical resection sampling, the 12-core method still has a false-negative rate of 10% to 20%.[28,29] This limitation made it impossible to calculate the true false-negative rates for the various biopsy methods in this study, thus underestimating the rates of misdiagnosis.

In conclusion, for patients receiving a biopsy for the first time, to maximize the detection rate of PCa and csPCa, 10- or 12-core biopsy showed a higher detection rate than the other schemes. For patients with a PSA concentration of 20 ng/mL or higher, the 6-core systematic biopsy is preferred, and the remaining cases can receive either the 10- or 12-core method.

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