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Is extended biopsy protocol justified in all patients with PSA ≥ 20 ng/mL?*

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Abstract ***Objective:*** The aim of this study was to investigate whether it was necessary to increase the number of cores at initial prostate biopsy with patients of prostate-specific antigen (PSA) ≥ 20 ng/mL and to explore an appropriate individualized transrectal ultrasonograhpy (TRUS)-guided prostate biopsy for the detection of prostate cancer in men suspicious of prostate cancer. ***Methods:*** A total of 115 patients with PSA ≥ 20 ng/mL and suspicious of prostate cancer were prospectively randomized to perform TRUS-guided biopsy. Patients were randomized to a "6 + X" cores or a "10 + X" cores protocol. The primary end point was cancer detection rate. Secondary end points were cancer characteristics, rate of complications and the level of pain experienced by patients during TRUS-guided prostate biopsy. ***Results:*** Preoperative variables were similar in both groups. The overall prostate cancer detection rate was 73.9%. The "10 + X" cores strategy increased cancer detection rate only 9.7% in patients with PSA ≥ 20 ng/mL but < 50 ng/mL, while there was no difference between the two strategies for cancer detection in patients with PSA ≥ 50.1 ng/mL. The number of extended biopsy cores and pain score of extended biopsy in prostate cancer patients increased significantly ($P < 0.001$). ***Conclusion:*** Our findings suggest that there is no significant advantage in using extended biopsy protocol in all patients with PSA ≥ 20 ng/mL.

Key words biopsy; prostate cancer (PCa); extend; detection rate; prostate-specific antigen (PSA)

Prostate-specific antigen (PSA) is prostate specific rather than cancer specific and therefore benign prostatic disease and especially benign prostatic hyperplasia (BPH) may also cause an increase in serum PSA. So, the diagnosis of prostate cancer depends on adequate tissue sampling of the prostate gland. Prostate biopsy techniques have changed significantly since the original Hodge's scheme [1]. With an aging population and routine use of PSA testing, there is an increase in men undergoing biopsy to assess for prostate cancer (PCa). Although the use of transrectal ultrasound (TRUS)-guided biopsy is considered the gold standard for the diagnosis of prostate cancer, the strategies for initial and repeat biopsies remain controversial, even with the widespread application of extended prostate biopsy protocols [2–4]. But, is extended biopsy protocol justified in all patients with PSA ≥ 20 ng/mL? In addition to this interesting result, the present study presents some limitations with the most obvious being that we do not know how many cancers were missed with either the 24 or 6 cores technique. Thus, The aim of this study was to clear whether it was necessary to increase the number of cores at initial prostate biopsy with the patients of PSA ≥ 20 ng/mL and to explore an appropriate individualized TRUS-guided prostate biopsy for the detection of PCa in men suspicious of prostate cancer.

Patients and methods

This was a prospective, randomized study conducted from January 2007 to December 2012. The 115 patients were selected and agreed to participate in the study. All patients' PSA ≥ 20 ng/mL. Indicators included patients age, PSA level, digital rectal examination (DRE), TRUS and pain score were shown in Table 1. All patients were administered cefaclor capsules (0.25 g) and metronidazole tablets (400 mg) twice a day, beginning three days before the procedure and continuing for three days afterwards.

The "6 + X" cores and "10 + X" cores protocols were used. The "6 + X" cores protocol consisted of sextant (the apex, middle, and base of each latral lobe para-sagittally) cores plus X and the "10 + X" protocol consisted of sex-

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tant cores and two cores from each lateral lobe plus X (Fig. 1). The "6" and "10" were all fixed puncture points. The additional samplings (X) in suspicious areas such as hypoechogenic areas or those with loss of capsular limits were about 1–4 cores, and it's not fixed. Each core was put a bottle and labeled. Samples were analyzed separately by the same pathologist to avoid inter-observer error. The results of biopsy histopathology were documented as malignant, benign, or prostatic intra-epithelial neoplasia (PIN). The overall histopathology from combination of two biopsy protocols' specimens termed "10 + X" was reported as well as the results of "6 + X" biopsies separately.

All patients were placed in the left lateral decubitus position. All the TRUS-guided prostate biopsy was carried out only liquid paraffin without any anaesthesia. Biopsies were performed with a spring-loaded biopsy gun (OptiMed Medizinische Instrumente GmbH, Germany) and 18-gauge biopsy needle (OptiMed Medizinische Instrumente GmbH, Germany) (Fig. 2). Immediately after the procedure, patients were asked about the discomfort or pain during the procedure including on insertion of the ultrasound probe (Shanghai Medical Instrument Co., Madison) and taking the biopsy, respectively. The scale was a visual analogue scale (VAS) (Fig. 3), scored as 0: no pain, 1 to 3: middle, 4 to 6: moderate, 7 to 9: severe and 10: worst pain that patients could imagine. All patients were asked by the same nurse.

A structured pro forma was used to obtain relevant patients' information including the examination findings, TRUS, results of PSA, indications for biopsy, pain score, and histopathology results. The data obtained from all patients on the pro forma were analyzed with Statistical Package for the Social Science (SPSS), version 16.0. The Mann-Whitney U non-parametric rank sum test was used to compare continuous variables and Pearson Chi-square test was used to compare dichotomous variables. *P*

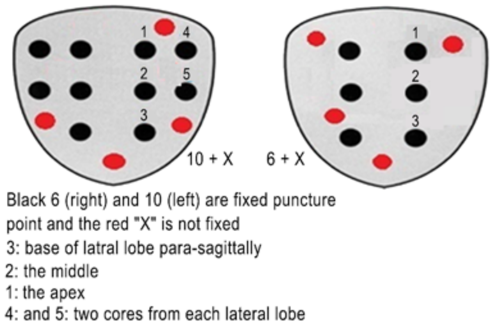

Fig. 1 The schematic diagram of "6 + X" cores and "10 + X" cores

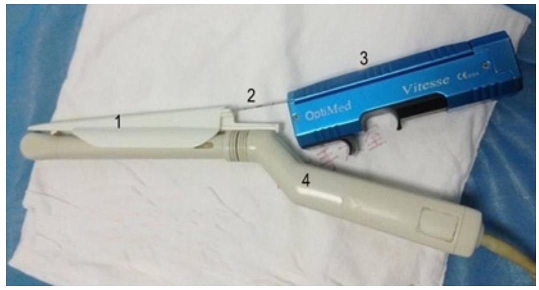

Fig. 2 Spring-loaded biopsy gun and 18-gauge biopsy needle. 1: puncture frame; 2: 18-gauge biopsy needle; 3: spring-loaded biopsy gun; 4: ultrasound probe

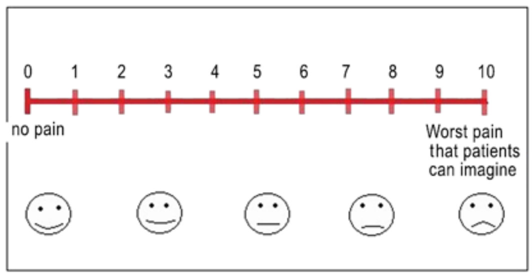

Fig. 3 Visual analogue scale (VAS)

Table 1 Patient characteristics according to biopsy outcome (prostate cancer vs non-prostate cancer)

	Prostate cancer	Non-prostate cancer	*P* value	Total (*n*)
No. of patients	85	30		115
The mean age (years)	77.1 ± 8.3	75.7 ± 6.7	0.218*	
The mean PSA (ng/mL)	170 ± 181.9	33.2 ± 16.5	< 0.000*	
PSA range (ng/mL) (%)			< 0.001**	
20–50	31 (52.5)	28 (47.5)		59
50.1–100	17 (89.5)	2 (10.5)		19
> 100	37 (100)	0		37
DRE (%)			< 0.001***	
Abnormal	74 (91.4)	7 (8.6)		81
Normal	11 (32.4)	23 (67.6)		34
TRUS (%)			< 0.001***	
Abnormal	83 (86.5)	13 (13.5)		96
Normal	4 (21.1)	15 (78.9)		19

* Mann-Whitney U test; ** Pearson χ^2-test; *** Chi-square test

Table 2 Prostate cancer detection rates of "6 + X" and "10 + X" cores biopsy strategies in patients with serum PSA ≥ 20 ng/mL

PSA range (ng/mL)	Cancer detection rates of two strategies (%)		Increase in cancer detection (%)	*P* value
	6 + X	10 + X		
20–50	28/59 (47.5)	31/59 (52.5)	3/31 (9.7)	< 0.001*
50.1–100	17/19 (89.5)	17/19 (89.5)	0	
> 100	37/37 (100)	37/37 (100)	0	
Total	82/115 (71.3)	85/115 (73.9)	3/85 (3.5)	< 0.001**

* Pearson χ^2-test; ** McNemar's test

Table 3 Comparison of pain score, the number of biopsy core and operation time of two strategies

	6 + X	10 + X	*P* value
Biopsy core number	7.4 ± 1.2	11.8 ± 1.4	0.000
Pain score on probe insertion (SD)	2.8 ± 0.9	2.8 ± 1.2	0.777
Pain score on TURS biopsy (SD)	4.0 ± 1.3	7.8 ± 1.0	0.000
Operation time (s)	1.1 ± 17.6	1.8 ± 21.4	0.000

McNemar's test

Table 4 Complications of two strategies (*n*)

	6 + X	10 + X	*P* value
Hematuria	7	9	< 0.005
Urinary tract infection	5	4	
Vasovagal reaction symptoms	3	3	
Urinary retention	3	5	
Rectal bleeding	1	0	

Chi-square test

< 0.05 was considered statistically significant.

Results

A total of 115 patients were enrolled for the study. The 85 (73.9%) of the 115 patients had malignant histology, 22 (19.1%) were prostatitis, while 8 (7.0%) had prostate intraepithelial neoplasm (PIN). In the malignant histology, one example of prostate small round cell tumor, one case of prostate mucus fibrosarcoma, and the rest of prostate adenocarcinoma.

Table 1 showed clinical characteristics of the PCa patients and the non-cancer patients. The mean age of PCa patients and non-prostate cancer patients were (77.1 ± 8.3) and (75.7 ± 6.7) years, respectively, and there were no statistically significant differences in baseline characteristics between the two groups ($P = 0.218$). Their mean PSA were (170 ± 181.9) ng/mL and (33.2 ± 16.5) ng/mL, respectively, and the abnormal DRE and TRUS findings were 81 (70.4%) and 96 (83.5%), respectively. From Table 1, abnormal DRE rate and abnormal TRUS rate were significantly higher in prostate cancer patients.

Table 2 showed that PCa detection rates of "6 + X" and "10 + X" cores biopsy strategies in patients with serum PSA ≥ 20 ng/mL. When the level of total prostate specific antigen (T-PSA) was between 20 and 50 ng/mL, the pathology results were 59 cases of PCa, 28 patients for "6 + X" and 31 for "10 + X", the positive rate were 47.5% and 52.5%, respectively. The increase of "10 + X" in cancer detection was only 9.7%. So, the method of "10 + X" had no advantage in increasing of cancer detection than "6 + X" when the T-PSA between 20 to 50 ng/mL. When the level of T-PSA ≥ 50.1 ng/mL, the positive rates were similar, and no significant differences. It would be seen from that the positive rate of "10 + X" than "6 + X" were falling in the level of T-PSA ≥ 20 ng/mL.

Table 3 showed that comparison of pain score, the number of biopsy core and operation time of two strategies. The biopsy core number of "10 + X" was significantly higher than "6 + X". Between the two groups, the average pain score at the time of insertion of the ultrasound probe were 2.8 ± 0.9 and 2.8 ± 1.2 and the average pain score at the time of taking biopsy were 4.0 ± 1.3 and 7.8 ± 1.0, respectively. The mean operation time were (1.1 ± 17.6) s and (1.8 ± 21.4) s, respectively. There were no significant differences between the two groups when the time of insertion of the ultrasound probe ($P = 0.777$), but the average pain score of "10 + X" at the time of taking biopsy were significantly higher than "6 + X". Certainly, with the increase in the number of puncture, inevitably prolonged operation time, that is, the operation time of "10 + X" was significantly higher than "6 + X".

In our group, there was only one (0.9%) major complication requiring hospitalization: that was one delayed severe rectal bleeding in the "6 + X" group. The patients recovered shortly after appropriate therapies. Other minor complications included hematuria in 13.9% (16/115), urinary tract infection in 7.8% (9/115), vasovagal reaction symptoms in 5.2% (6/115) and urinary retention in 7.0% (8/115) of patients. Between the two groups, there were significant differences ($P < 0.005$). Patients with minor complications were treated as outpatients and recovered quickly (Table 4).

Discussion

The major tools for diagnosis of PCa include the PSA level, digital rectal examination (DRE) and prostate biopsy [5]. DRE is found most helpful in diagnosis of PCa first line checks, but about 1/4 of the peripheral zones occur in the transition zone tumors and 20% of the tumor, the higher position, difficult to reach, and, DRE for diameter < 0.5 cm nodule sensitivity is not high [6]. So, DRE is notoriously inaccurate. Whereas DRE has a roughly 30% positive predictable value for PCa. Therefore, despite its low positive predictive value, DRE is still recommended as part of the routine screening regimen. With this interesting result, we try to increase the area of abnormal DRE biopsy needles. And, our previous studies have shown that increasing the number of abnormal DRE biopsy area, can significantly improve the positive biopsy rate [7]. So, we believe that an appropriate increase the number of abnormal DRE puncture area, help to improve the detection rate of prostate.

Notably, PSA testing continues to be one of the most controversial topics in cancer screening. PSA is widely accepted as a prostate cancer tumour marker, but it is organ specific and not disease specific, and PSA's low positive predictive value, up to 75% of men with levels in the range of the 2.5–10 ng/mL and/or suspicious DRE findings still have negative biopsies [8]. So, early studies that established the reference range of ≤ 4.0 ng/mL to define normal serum PSA levels would recommend further evaluation to rule out prostate cancer is controversial.

Although the TRUS-guided prostate biopsy is the gold standard for diagnosing prostate cancer, the best strategy for biopsy remains controversial [9]. However, some researchers have demonstrated that the traditional sextant biopsy strategy is insufficient for diagnosing prostate cancer as compared with the extended biopsy strategies (ranging from eight to 26 cores), which detect probably 30% more cancers without increasing the number of clinically insignificant cancers [10–14]. However, they all have a fatal flaw, that is, for different levels of PSA using the same program. We all know that when PSA < 20 ng/mL, the appropriate increase in the number of needle can significantly improve the detection rate of prostate cancer, but for PSA ≥ 20 ng/mL, if the protocol is still in this way, whether the patients are not fair?

With the above controversy, in this study, we used "6 + X" and "10 + X" cores biopsy strategies to biopsy for the patients with PSA ≥ 20 ng/mL, confirmed to whether it was necessary to increase the number of cores when PSA ≥ 20 ng/mL.

In the past 6 years, we have performed TRUS-guided "6 + X" and "10 + X" cores biopsy in 115 patients with PSA ≥ 20 ng/mL. The overall cancer detection rate was 73.9%, and the abnormal DRE rate and abnormal TRUS rate were significantly higher in our cancer patients than in non-cancer patients. In this subset, when the level of T-PSA between 20 and 50 ng/mL, the "6 + X" technique detected 28 cancers while the "10 + X" technique detected a total number of 31 cases. This is a 9.7% increase in prostate cancer detection rate by addition of the four lateral biopsies in this category of patients, it was found to be no significant. However, for PSA ranged above 50 ng/mL, cancer detection rate were not affected by increased number of cores. Many developed-world studies investigating the diagnostic value of the extended prostate biopsy strategies seldom consider the effect of patient's PSA level on cancer detection improvement [9, 15–16]. Some studies investigated by this review only included patients with PSA < 10 ng/mL, or with PSA < 20 ng/mL, the reason of the proportion of patients with PSA > 20 ng/mL was very low in those developed-world studies. However, many such people in China, may be the Chinese people less willing to follow the routine physical examination related.

Nowadays, with the development of prostate biopsy, ultrasound-guided transrectal needle biopsy of prostate has significantly improved the diagnosis and treatment of prostate cancer. Many Studies [17–18] have demonstrated that a traditional sextant technique may miss substantial numbers of cancers. But, is extended biopsy protocol justified in all patients with PSA ≥ 20 ng/mL? In our study, we compared "6 + X" core with "10 + X" core biopsies for the patients with PSA ≥ 20 ng/mL, we found that when the level of T-PSA between 20 and 50 ng/mL, compared to the "6 + X", the increase of "10 + X" in cancer detection was only 9.7%. And when the levels of T-PSA ≥ 50.1 ng/mL, the positive rates were similar, and no significant differences. Compared the number of "6 + X" core and "10 + X" core biopsies, we found that the "10 + X" group was significantly higher than "6 + X" group, simultaneously, along with the increase in the number of puncture, the patient experienced pain and duration of operation was significantly increased. This shows, when the patient PSA ≥ 20 ng/mL, no need to use to expand puncture.

TRUS-guided prostate biopsy is the most commonly used procedure for detecting prostate cancer. However, pain is the main morbidity and the main hindrance to the acceptance of TRUS-guided prostate biopsy by patients, especially those initial negative biopsy patients need a repeat biopsy. Brock M *et al* [19] showed that 19% to 30% of patients experience moderate to severe pain during prostate biopsy, some researchers [20–21] have demonstrated that extended biopsy protocol is associated with increased pain, discomfort, and anxiety. The most likely reason is that the pain, including transrectal probe insertion and when the needle pierces the capsule of the prostate through the rectal wall. In our study, the mean pain VAS scores during probe insertion were 2.8 ± 0.9, and 2.8 ± 1.2 in groups "6 + X" and "10 + X", respectively, and there were no statistically significant differences between the two groups (P = 0.777). The mean pain VAS scores during prostate biopsy were 4.0 ± 1.3 and 7.8 ± 1.0 in groups "6 + X" and "10 + X", respectively, the "10 + X" group was significantly higher than "6 + X" group ($P = 0.000$).

Conclusions

Despite the expansion of the puncture did not increase the incidence of complications, but the increasing number core have significantly increases the patient's pain discomfort, and, for the patients of PSA ≥ 20 ng/mL, puncture positive rate is not greatly improved, therefore, for such patients, the traditional sextant and appropriate increase in suspicious areas puncture are enough.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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