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The best prostate biopsy scheme is dictated by the gland volume: a monocentric study

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Abstract. – OBJECTIVE: Accuracy of biopsy scheme depends on different parameters. Prostate-specific antigen (PSA) level and digital rectal examination (DRE) influenced the detection rate and suggested the biopsy scheme to approach each patient. Another parameter is the prostate volume. Sampling accuracy tends to decrease progressively with an increasing prostate volume. We prospectively observed detection cancer rate in suspicious prostate cancer (PCa) and improved by applying a protocol biopsy according to prostate volume (PV).

PATIENTS AND METHODS: Clinical data and pathological features of these 1356 patients were analysed and included in this study. This protocol is a combined scheme that includes transrectal (TR) 12-core PBx (TR12PBx) for PV ≤ 30 cc, TR 14-core PBx (TR14PBx) for PV > 30 cc but < 60 cc, TR 18-core PBx (TR18PBx) for PV ≥ 60 cc.

RESULTS: Out of a total of 1356 patients, in 111 (8.2%) PCa was identified through TR12PBx scheme, in 198 (14.6%) through TR14PBx scheme and in 253 (18.6%) through TR18PBx scheme. The PCa detection rate was increased by 44% by adding two TZ cores (TR14PBx scheme). The TR18PBx scheme increased this rate by 21.7% vs. TR14PBx scheme. The diagnostic yield offered by TR18PBx was statistically significant compared to the detection rate offered by the TR14PBx scheme ($p < 0.003$). The biopsy Gleason score and the percentage of core involvement were comparable between PCa detected by the TR14PBx scheme diagnostic yield and those detected by the TR18PBx scheme ($p = 0.362$).

CONCLUSIONS: The only PV parameter, in our opinion, can be significant in choosing the best biopsy scheme to approach in a first setting of biopsies increasing PCa detection rate.

Key Words:
Prostate cancer, Prostate biopsy, Detection rate, Prostate volume, Transrectal ultrasound.

Introduction

Prostate cancer (PCa) is the most frequent tumor diagnosed in elder man counting about 340.000 new diagnosis per year in the European Union[1] and about 1 million biopsies per year performed in the United States[2]. The role of prostate biopsy (PBx) has shifted from mere cancer detection to the characterisation of cancer type to assist in the clinical management of patients, including active surveillance[3]. Systematic PBx scheme under transrectal ultrasound (TRUS), as the gold standard technique for PCa detection, has been constantly modified in order to increase the PCa detection rate[4]. The systematic sextant biopsy protocol introduced by Hodge et al[5] was unacceptable due to high false-negative rate, so that extended prostate biopsy schemes were introduced[6]. Several authors indicated the benefits of a PBx containing > 18 cores as an initial strategy[7,8], whereas other teams did not recommend saturation PBx for cancer detection improvement[9,10]. Nevertheless, accuracy of biopsy scheme depends on different parameters. Prostate-specific antigen (PSA) level and digital rectal examination (DRE) influenced the detection rate and suggested the biopsy scheme to approach each patient[11]. Another parameter is the prostate volume. Sampling accuracy tends to decrease progressively with an increasing prostate volume[11-14]. The inclusion of patients in active surveillance protocols emphasizes the necessity of accurate staging strategies. In the present study evaluated PCa detection rates were improved according prostate volume and justified extending biopsy protocol to all patients with suspected PCa.

Patients and Methods

Between September 2007 and May 2014, 1356 consecutive patients suspicious for PCa with serum PSA levels in the range 2.5-20 ng/mL or abnormal DRE underwent initial PBx a TRUS-guided protocol. This protocol is a combined scheme that includes transrectal (TR) 12-core PBx (TR12PBx) for prostate volume (PV) ≤ 30 cc, TR 14-core PBx (TR14PBx) for PV > 30 cc but < 60 cc, TR 18-core PBx (TR18PBx) for PV ≥ 60 cc.

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The biopsy procedure was performed by three experienced urologists. Patients on anticoagulation/antiplatelet therapy were considered eligible for the study, providing they had followed the instructions of stopping antiplatelet drugs at least 5 days before the biopsy, or stopping anticoagulation drugs and replacing them with low molecular weight heparin at least 5 days before the biopsy. Patients were instructed to take antibiotics, usually levofloxacin 500 mg orally, for 5 days starting the evening before the procedure and a small evacuative enema starting two hours before the procedure. All procedures were performed in order to empty the bladder, since we believe that even the state of bladder repletion may be an element of discomfort during the performance of mapping biopsy. Each patient was treated under local anaesthesia with Lidocaine Spray (10 g/100 ml), applied two minutes before the procedure[15] or general anaesthesia. PBx was performed with the patient in the left lateral decubitus using an General Electric Logiq 7 machine equipped with a 5-9MHz multi-frequency convex probe "end-fire". The biopsy protocol included prostate ultrasound examination to evaluate the prostate volume using the prostate ellipsoid formula (0.52 × width × length × height).

Each transrectal ultrasound performed included an assessment of the prostatic diameter (maximal transverse dimension, maximal antero-posterior dimension, maximal supero-inferior dimension), the volume of the whole prostate, the transition zone, capsular and seminal vesicle characteristics, as well as morphological description of potential pathological features.

After the prostate imaging, sampling was carried out with a 18-Gauge Tru-Cut needle powered by an automatic spring-loaded biopsy disposable gun.

To analyze the biopsy scheme and cancer location the prostate was divided into apex, mid-prostate and base regions. TR12PBx scheme included the sextant biopsies (apex, middle, and base of each lateral lobe) and the six additional lateral peripheral biopsies. TR14PBx scheme was obtained by adding to the previous one the transition zone (TZ) of each lateral lobe. TR18PBx scheme instead added to TR12PBx six TZ cores. All biopsy specimens were pathologically analysed by at least two genitourinary pathologists. Clinicopathologic characteristics of PCa diagnosed or missed by each biopsy scheme were also assessed and compared.

Statistical Analysis

The normal distribution of continuous variables were reported as mean and standard deviation. For independent parameters, the Student *t* test was used for quantitative variables and Chi-square analysis (or Fisher's exact test, as appropriate) was used for qualitative variables. A $p < 0.05$ was considered to indicate statistical significance.

Results

Out of an amount of 1356 patients, in 111 (8.2%) PCa was identified through TR12PBx scheme, in 198 (14.6%) through TR14PBx scheme and in 253 (18.6%) through TR18PBx scheme. The mean age of patients with benign prostatic hyperplasia (BPH) was 63.4 ± 7.8 and the mean age of the patients with PCa was 65.4 ± 8.1 ($p = 0.286$). While the median PV in the BPH was 54 cc (range: 19-120), the median PV in PCa was 38 cc (range: 22-145) ($p < 0.001$). The patient characteristics are listed in Table I. The PCa detection rate was increased by 44% by adding two TZ cores (TR14PBx scheme). The TR18PBx scheme increased this rate by 21.7% vs. TR14PBx scheme (Table II). Therefore, the detection cancer rate has been increased to a greater number of cores taken ($p < 0.001$), regardless to the PV increasing. The diagnostic yield offered

Table I. Characteristics of the entire patient cohort who underwent prostate biopsy.

Patients characteristics (n = 1356)	
Age (yrs), mean ± SD	63.4 ± 8.1
Positive family history, n. (%)	247 (18.2)
Mean prostate volume, cc	48.3 (19-145)
Mean PSA level, ng/mL	6.8 (2.5-20)
Mean free-to-total PSA, %	16.4 (7-32)
Abnormal DRE, n. (%)	411 (30.3)
HG-PIN, n. (%)	72 (5.3)
ASAP, n. (%)	64 (4.7)
PCa cases, n. (%)	562 (41.5)
Biopsy Gleason score, n. (%)	
≤ 6	402 (71.5)
= 7	97 (17.2)
≥ 8	63 (11.2)
Mean positives cores, n.	5.5 (2-9)

SD = standard deviation; PSA = prostate-specific antigen; DRE = digital rectal examination; HG-PIN = high-grade prostatic intraepithelial neoplasia; ASAP = atypical small acinar proliferation; PCa = prostate cancer.

Table II. Prostate cancer detection of 12-, 14-, and 18-core biopsy scheme.

Patients (n = 1356)	PCa cases n°	PCa detection rate (%)	*p* value
Diagnosis based on:			
TR12PBx scheme	111	8.2	
TR14PBx scheme	198	14.6	
TR18PBx scheme	253	18.6	
Diagnostic yield, n°			
14 vs 12 cores		+44.0	< 0.001
18 vs 12 cores		+56.1	< 0.001
18 vs 14 cores		+21.7	< 0.001

TR(n) PBx = transrectal (n)-core prostate biopsy; PCa = prostate cancer.

by the TR18PBx was statistically significant compared with the detection rate offered by the TR14PBx scheme ($p < 0.003$). The biopsy Gleason score and the percentage of core involvement were comparable between PCa detected by the TR14PBx scheme diagnostic yield and those detected by the TR18PBx scheme ($p = 0.362$). Anaesthetic methods applied were general anaesthesia in 287 patients, local anaesthesia in 1069 patients and when stratified by anaesthetic methods, the overall cancer detection rate was 35.5% (102/287) in patients with general anaesthesia, 43% (460/1069) with local anaesthesia. There was no statistical difference in detection rate between the different anaesthetic methods ($p = 0.232$). Biopsy-related complications requiring prolonged hospital stay or re-hospitalisation during two weeks post-biopsy were observed in 19 patients (1.4%), including 8 patients with acute bacterial urinary infection (2: TR12PBx, 4: TR14PBx, 2: TR18PBx), 3 with acute urinary retention (3: TR18PBx), 5 with rectal bleeding (2: TR14PBx, 3: TR18PBx), 3 with urethral bleeding (3: TR18PBx). All complications were successfully managed conservatively.

Discussion

Over the last few years, interest has increased in defining more efficient biopsy schemes for PCa detection[16,17]. The best cores scheme that should be obtained with a prostate biopsy remains unclear, many studies have shown that extended prostate biopsies are superior to sextant protocols in the PCa detection[18-20]. Nevertheless, the role of extended biopsy scheme as initial strategy is controversial. Eichler et al[21] showed that no significant benefit accrues by taking > 12 cores, and Jones et al[22] suggested that further efforts at extended biopsy scheme beyond 10-12 cores are not appropriate in the initial setting. Numerous predictive factors for appropriate initial protocol for TR prostate biopsy including PSA, age, positive fami-

Table III. Clinicopathologic features of patients with prostate cancer detected by each biopsy scheme.

Patients with PCa (n = 562)	TR12PBx scheme (n = 111)	TR14PBx scheme (n=198)	TR18PBx scheme (n = 253)
Age (yrs), mean ± SD	63.2 ± 7.1	65.4 ± 8.3	64.2 ± 7.6
Positive family history, n. (%)	39 (35.1)	61 (30.8)	82 (32.4)
Mean prostate volume, cc	28.1 (17-30)	43.3 (32-58)	62.5 (60-145)
Mean PSA level, ng/mL	6.7 (2.5-17)	7.2 (2.2-20)	6.9 (3.2-19)
Mean free-to-total PSA,%	15.8 (7-21)	16.2 (8-32)	16.3 (9-27)
Abnormal DRE, n. (%)	62 (55.9)	118 (59.6)	137 (54.1)
Biopsy Gleason score, n. (%)			
≤ 6	87 (78.4)	113 (57)	202 (79.9)
= 7	21 (18.9)	37 (18.7)	39 (15.4)
≥ 8	13 (11.7)	19 (9.6)	31 (12.3)
Mean positives cores, n.	5.5 (2-6)	6.2 (2-7)	6.9 (2-8)

TR(n)PBx = transrectal (n)-core prostate biopsy; SD = standard deviation; PSA = prostate-specific antigen; DRE = digital rectal examination; PCa = prostate cancer.

ly history ($p < 0.001$), abnormal DRE findings and PV have been reported[3,4,8,12,13] in numerous studies. Of these only a few examining PV are available. Guichard et al[23] divided the PV into three groups: < 35 cc, 35-55 cc, and > 55 cc; cancer detection rates were 45%, 36%, and 28%, respectively, when a 12-core biopsy was taken. Moreover, in this study, the author found that PV was significantly low in the positive biopsy (39.7 vs. 46.8 cc, $p < 0.01$). Turley et al[24] observed that patients with PV 20 cc or less had more than five times the risk of disease respect to patients with PV more than 60 cc. Kassout et al[25] reported that the incidence of PCa was significantly higher in men with a PV greater than 50 cc compared to that in those with a larger PV. Al-Azab et al[26] also observed that smaller PV was associated with PCa patients with PSA 2.0-9.0 ng/mL. TRUS is widely used to calculate PV and is considered a reliable technique to estimate prostate size, with an accuracy within 20% of pathological weight[27,28]. Moreover, a significant PV variation between intra-observer of TRUS measurement could also exist even among highly experience radiologists. In the present study we analysed prospectively the diagnostic performance and safety of an extended prostate biopsy scheme in relation to the prostate gland volume. In our study the TR18PBx extended to TZ and midline prostate gland had a detection rate increased by 21.7%. Regarding these results obtained, the PV was identified as a significant predictive factor of PCa detection. However, we think that patients with larger PV have increased PSA levels driven by BPH and, therefore, are likely to be referred for PBx sooner than other patients[29]. In addition to this, due to the small volume of tumors in large prostates, the increasing number of cores may lead to an increased detection rate of PCa. However, several limitations need to be acknowledged. A first limitation of our study concerns the race: all the participants are white, therefore results might not be generalizable to other races and the patients were selected from a single hospital. Second, we only observed the first prostatic biopsy. We were not able to reflect the results of repeated biopsies due to a considerable number being lost during follow-up. Zaytoun et al[30] have observed at Cleveland Clinic the saturation PBx in a heterogeneous population of patients undergoing repeated biopsies after a single prior biopsy that failed to diagnose PCa. They showed that saturation PBx detected almost one-third more cancers. In men with BPH, saturation PBx demonstrated significantly greater PCa detection. Scattoni et al[10] demonstrated that the number of biopsy cores affect cancer detection rate in a repeated biopsy setting. They also showed that the "optimal" repeat PBx scheme varies according to the clinical characteristics of patients. Thus our study is influenced by verification bias because we cannot define the real diagnostic accuracy of our combinations of schemes since it is not possible to perform radical prostatectomy in all these patients.

Conclusions

All of these data demonstrate that cancer detection is influenced not only by the number of cores but also by the PV and when PV increases, the core numbers should be increased in first PBx setting. This parameter alone can be significant in choosing the best biopsy scheme to approach in a first setting of biopsies in order to increase the detection rate of PCa. We propose a simply method to identify an optimal biopsy strategy for patients with suspected PCa. Certainly randomized clinical trials will be essential to establish the efficacy of the best PBx scheme treatment regimen.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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