Transrectal ultrasound-guided prostate rebiopsy: How many core sampling should be applied to which patient?

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Abstract

Background: We investigated the correlation between the sampled number of cores in rebiopsy and the cancer detection rate (CDR).

Materials and Methods: Two hundred and twelve patients with normal rectal examination who had undergone rebiopsy in the past 5 years were examined retrospectively. Moreover, 68% of them had undergone 12 cores (Group 1) while 32% had undergone 20 cores (Group 2). Both groups were compared with respect to the CDR.

Results: There was no difference between groups in terms of age, total prostate-specific antigen, and prostate volume ($P > 0.05$). Forty-one (19%) of 212 patients were diagnosed with cancer, and the CDR was significantly higher in Group 2 (30.9% vs. 13.9%, $P = 0.004$). This rate increased from 6.5% to 20% ($P = 0.025$) and from 0% to 33.3% ($P = 0.023$), respectively, with 12-core and 20-core rebiopsies in patients whose initial pathology indicated benign and high-grade prostatic intraepithelial neoplasia (HGPIN). Furthermore, cancer was detected in 24 (40%) of 60 patients who were diagnosed with atypical small acinar proliferation (ASAP) in the initial biopsy. However, despite being higher in 20-core biopsy group (47.6% vs. 35.9%), this was not statistically significant ($P = 0.377$).

Conclusions: At least 20 cores should be sampled in rebiopsy, especially in the patients diagnosed with benign and HGPIN. However, we believe that standard systematic sampling will be sufficient for the patients diagnosed with ASAP.

Keywords: Atypical small acinar proliferation, prostate cancer, transrectal ultrasound prostate rebiopsy

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed nonskin cancer and the sixth leading cause of cancer death in males around the world.[1,2] The incidence is higher in the developed countries, and the 12-core systematic transrectal ultrasound (TRUS)-guided biopsy is the standard method for the diagnosis of PCa. The indications of prostate biopsy are high serum total prostate-specific antigen (PSA) levels and/or suspicion in digital rectal examinations (DRE). PCa is determined in approximately

Access this article online

Quick Response Code:

Website:
www.urologyannals.com

DOI:
10.4103/UA.UA_110_17

How to cite this article: Amasyali AS, Yücetaş U, Erkan E, Demiray M, Karabay E, Murat C, *et al.* Transrectal ultrasound-guided prostate rebiopsy: How many core sampling should be applied to which patient?. Urol Ann 2018;10:15-9.

25% of the patients who undergone first TRUS-guided biopsy; however, the studies estimate that up to 47% of cancer cases may not be detected in the initial biopsy.[3,4] Patients with previously negative biopsy results should undergo rebiopsy in cases of elevated PSA, suspected DRE, atypical small acinar proliferation (ASAP), extensive high-grade prostatic intraepithelial neoplasia (HGPIN), and positive multiparametric magnetic resonance imaging (MRI) findings.[5]

An increasing number of data have shown the value of MRI-targeted rebiopsy. Clinically, significant rate of cancer detection varies between 11% and 54% on MRI-targeted biopsy in the rebiopsy setting. However, 5%–15% of the clinically significant cancer cases remain undetected in these patients. Furthermore, this technique cannot be used widely, especially in the developing countries because of its cost and time requirements during the procedure.[6] Moreover, it is recommended that concurrent systematic sampling at the time of targeted biopsy with MRI should be performed to increase the chance of clinically significant cancer detection as well.[7] That's why systematic biopsy still maintains its clinical importance.

In general, PCa is detected between the rate of 10% and 25% in patients who undergone rebiopsy.[8] Moreover, this rate depends on the previously reported histopathological findings and the number of core sampled during rebiopsy. The present study compares the cancer detection rates (CDRs) in terms of the different number of sampled cores in rebiopsy. We have also investigated whether the higher number of sampled cores increases CDRs in systematic rebiopsy, especially in cases with ASAP on the previous biopsy.

MATERIALS AND METHODS

A total of 212 patients who had rebiopsy because of rising or persistently elevated PSA and/or suspected histopathology in initial biopsy were enrolled in the study between the years 2011 and 2016. All procedures were conducted in the same academic tertiary referral center (Istanbul Training and Research Hospital, Department of Urology), and only patients with normal DRE were included in the study. All patients were informed of the prostate biopsy and its potential complications, and informed consent for the procedure was signed by all patients.

The earliest repeat biopsy was held in the 6 months after the initial biopsy. Prostate biopsies (PBx) were carried out under the guidance of transrectal ultrasonography. As per our prostate biopsy protocol, an antibiotic treatment started

2 days before the procedure and it was recommended to continue this treatment for 3 days after the procedure. A rectal enema was applied 1–2 h before the biopsy procedure to obtain good ultrasound imaging and to avoid infection.

The histopathological evaluation of the initial biopsy had been reported as follows: benign, HGPIN, and ASAP. The number of sampled cores in rebiopsy was 10–12 in 68% (*n* = 144, Group 1) of all patients and 18–20 cores in remaining 32% (*n* = 68, Group 2). Comparison was done between these two groups in terms of CDR retrospectively.

Statistical analysis
SPSS® 16.0 software (SPSS Inc; Chicago, IL, USA) was used for statistical analysis. A one-way ANOVA test was used to compare the ages, prostatic volumes, and serum total PSA levels of patients according to the number of biopsy cores performed. Chi-square test was used to analyze the differences in CDRs for the 10-12-PBx and 18-20-PBx groups. $P < 0.005$ was accepted as statistically significant.

RESULTS

One hundred and forty-four patients were had 10–12-core rebiopsy (Group 1) and 68 patients were had 18–20-core rebiopsy (Group 2). Histopathological evaluation of the initial biopsy of all these patients (*n* = 212) had been reported as follows: benign (*n* = 127), HGPIN (*n* = 25), and ASAP (*n* = 60).

The median age, total PSA, and prostate volume of Group 1 and Group 2 were 63 (10) (48–75) years, 7.24 (5.4) (3.3–43) ng/mL, and 44.75 (25) (15–119) mL and 62 (11) (41–77 years, 6.62 (5.3) (2.9–58.9) ng/mL, and 40 (25) (18–123) mL, respectively. No significant difference was found between the groups, and they were similar in respect to the above-mentioned parameters. All baseline demographics and clinical characteristics were given in Table 1.

Overall CDR was 19% (41/212). According to initial histopathological subgroups, the rate of cancer detection for benign, HGPIN, and ASAP was 10.2%, 16%, and 40%, respectively ($P < 0.0001$) [Table 2].

Furthermore, CDR was 13.9% in Group 1 while it was 30.9% in Group 2. We found a statistically significant difference between these groups ($P = 0.004$) [Table 3]. PCa was detected in 40% (24/60) of all patients whose initial prostate biopsy had been reported as ASAP. Moreover, again higher CDRs were noted in Group 2 compared to Group 1 in this specific patient group; however, it was

Table 1: Comparison of baseline demographics and clinical characteristics

	10-12-core rebiopsy	20-core rebiopsy	P
Age (years), median (IQR) (minimum-maximum)	63 (10) (48-75)	62 (11) (41-77)	0.908*
BMI (kg/m²), median (IQR) (minimum-maximum)	26.52 (4.78) (18.94-42.97)	26.42 (3.6) (20.52-34.6)	0.906*
Total PSA (ng/mL), median (IQR) (minimum-maximum)	7.24 (5.4) (3.3-43)	6.62 (5.3) (2.9-58.9)	0.188*
Percentage PSA ratio, median (IQR) (minimum-maximum)	0.17 (0.13) (0.03-0.44)	0.17 (0.13) (0.06-0.38)	0.771*
PV (mL), median (IQR) (minimum-maximum)	44.75 (25) (15-119)	40 (25) (18-123)	0.088*
PSAD, median (IQR) (minimum-maximum)	0.17 (0.15) (0.04-0.8)	0.16 (0.19) (0.04-1.03)	0.669*
Histopathology of initial biopsy, *n* (%)			
Benign	92 (63.9)	35 (51.5)	0.114**
HGPIN	13 (9)	12 (17.6)	
ASAP	39 (27.1)	21 (30.9)	

*Mann-Whitney U-test, **Chi-square test. BMI: Body mass index, PV: Prostate volume, PSAD: PSA density, HGPIN: High-grade prostatic intraepithelial neoplasia, ASAP: Atypical small acinar proliferation, PSA: Prostate-specific antigen, IQR: Interquartile range

not significant at all (47.6% vs. 35.9%, *P* = 0.377). On the other hand, CDRs were significantly higher when 20-core rebiopsy was performed in patients whose initial histopathology had been reported as benign and HGPIN. All CDRs of Group 1 and Group 2 are given in Table 4 according to their initial prostate biopsy results.

DISCUSSION

The current study demonstrates that higher CDRs can be achieved by sampling 20 cores in rebiopsy, especially in patients who had benign or HGPIN in their initial biopsy. We found that the CDR increased when 20-core rebiopsy was performed in all three histopathological subgroups, independently from age, PSA, or prostate volume of patients. However, the increase in the CDR was statistically insignificant in ASAP group.

Our cohort consisted of patients with normal DRE which indicated probable clinically T1c candidates. There is no consensus about the definite indication and optimal protocol for rebiopsy in this patient group. Although PCa detection rate varies between 10% and 25% in rebiopsy,[8] this rate could reach up to 41% in the previous negative biopsy series according to the initial histopathological findings.[9,10] The most suspicious histopathological finding is ASAP which presents a rate between 1.5% and 24% in TRUS biopsy. It is hard for pathologist to decide ASAP and its potential for cancer. Therefore, rebiopsy should be done in these patients to rule out PCa. In these cases, CDR varies between 19% and 38%, which depends on the number of the sampled cores used in rebiopsy.[11,12]

The previous data showed that >12-core biopsy contributes no significant benefit to the CDR in initially performed TRUS biopsy.[13-16] However, increasing the number of cores used in rebiopsy is controversial. Stewart *et al.* revealed that CDR increased to 30%–34% when the cores were obtained with saturation technique in rebiopsy.[17] However, in this study, sextant sampling was used in initial biopsy;

Table 2: Distribution of cancer detection rate between initial histopathological subgroups

	Cancer detection	P
Benign, *n* (%)	13 (10.2)	<0.0001
HGPIN, *n* (%)	4 (16)	
ASAP, *n* (%)	24 (40)	

Chi-square test. HGPIN: High-grade prostatic intraepithelial neoplasia, ASAP: Atypical small acinar proliferation

Table 3: Comparison of histopathological findings between groups

	10-12 core-rebiopsy	20-core rebiopsy	P
Benign, *n* (%)	110 (76.4)	36 (52.9)	0.004
HGPIN, *n* (%)	6 (4.2)	7 (10.3)	
ASAP, *n* (%)	8 (5.6)	4 (5.9)	
Cancer, *n* (%)	20 (13.9)	21 (30.9)	

Chi-square test. HGPIN: High-grade prostatic intraepithelial neoplasia, ASAP: Atypical small acinar proliferation

Table 4: Comparison of cancer detection rate according to initial histopathological findings between groups

	10-12-core rebiopsy	20-core rebiopsy	P
Benign, *n* (%)	6 (6.5)	7 (20)	0.025
HGPIN, *n* (%)	0	4 (33.3)	0.023
ASAP, *n* (%)	14 (35.9)	10 (47.6)	0.377

Chi-square test. HGPIN: High-grade prostatic intraepithelial neoplasia, ASAP: Atypical small acinar proliferation

therefore, more missing cancer cases were likely to be diagnosed during rebiopsy. Another supporting data by Presti concluded that at least 14-core biopsy should be taken during rebiopsy after a negative first biopsy.[18] Terris also advocated 14 cores for rebiopsy and recommended an additional biopsy with saturation technique if it was still negative.[19]

The National Comprehensive Cancer Network recommends an individualized rebiopsy decision for each patient based on the risk stratification factors such as PSA, PCA3, as well as percent-free PSA and prostate volume.[20] However, these parameters were similar in our cohort, and these patients had normal DRE. Nevertheless, we found a significantly increased CDR in Group 2 which means that the higher

number of sampled core in rebiopsy could achieve increased CDRs regardless of PSA and prostate volume. Recently, published data showed that the sampled >20 cores was associated with a higher likelihood of PCa diagnosis as consistent with our data.[21] Furthermore, these data indicated that patients older than 70 years and the fourth TRUS biopsy were associated with higher CDRs as well. However, they stated that early consideration of saturation or MRI-guided targeted biopsy may be required in the rebiopsy setting appropriately.

Previous studies have suggested that adding the multiparametric MRI-guided targeted biopsy to the systematic biopsy could improve CDRs with a set number of cores instead of higher number of biopsy cores.[22,23] It was also demonstrated that the multiparametric MRI-guided targeted biopsy increased not only clinically significant but also overall CDRs in patients with prior biopsy.[24-26] Likewise, MRI-ultrasound fusion-guided targeted biopsy may decrease the multiple rebiopsy requirements and prevent the complications of prostate biopsy. However, this technique is not broadly used in every clinic appropriately. Moreover, it not only increases the cost of procedure but also does not eliminate the need for a systematic prostate biopsy.

In clinical practice, we suppose that prostate biopsy protocols should be introduced for each patient to minimize missing cancer without significant morbidity. In this regard, Scattoni *et al.* developed an individualized approach with respect to the clinical characteristics of the patients.[27] Their study demonstrated that the optimal sampling for patients with or without previous ASAP diagnosis and <10% fPSA% (free PSA %), and two different combinations of a 14-core biopsy scheme (with or without transitional zone sampling) were most advantageous. On the other hand, if patients had previously no ASAP and fPSA% as >10%, 20-core biopsy was the most advantageous scheme. Thus, they could reach the similar CDRs with 24-core systematic biopsy. In consistent with this finding, we also found significantly increased CDRs in previously benign or HGPIN-diagnosed patients regardless of PSA and its derivatives when 20 cores were taken in rebiopsy.

The present study has some drawbacks in its retrospective nature. First, our cohort was heterogeneous in terms of initial histopathological evaluations. Second, we did not assess the area that should be sampled in case of the prostate. Moreover, we have not classified the detected PCa as clinically significant (Gleason >6) and clinically insignificant (Gleason <7). However, it was not within the scope of the current study.

CONCLUSIONS

We suggest that if rebiopsy is indicated for the patients with previously benign or HGPIN diagnosis in initial biopsy, higher number of cores should be sampled regardless of PSA and prostate volume even if DRE is normal. ASAP is another important factor influencing the decision-making process to perform rebiopsy since the CDR for ASAP is two times higher than the other pathological results in 20-core rebiopsy. However, the individualized approach and optimal scheme should be implemented with respect to characteristics of the patients.

Conflicts of interest
There are no conflicts of interest.

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