Longer biopsy cores do not increase prostate cancer detection rate: A large-scale cohort study refuting cut-off values indicated in the literature

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ABSTRACT

Objective: Only a few papers in the literature aimed to evaluate biopsy core lengths. Additionally, studies evaluated the core length with different approaches. We aimed to determine whether prostate cancer (PCa) detection is affected from core lengths according to three different approaches in a large standard cohort and compare our cut-off values with the published cut-offs.

Material and methods: We retrospectively analyzed 1,523 initial consecutive transrectal ultrasound-guided 12-core prostate biopsies. Biopsies were evaluated with respect to total core length (total length of each patients' core) average core length (total core length divided by total number of cores in each patient), and mean core length (mean length of all cores pooled), and compared our cut-off values with the published cut-offs. The prostate volumes were categorized into four groups (<30, 30-59.99, 60-119.99, ≥120 cm³) and PCa detection rates in these categories were examined.

Results: PCa was found in 41.5% patients. There was no difference between benign and malignant mean core lengths of the pooled cores ($p>0.05$). Total core length and average core length were not significantly associated with PCa in multivariate logistic regression analyses ($p>0.05$). The core lengths (mean, average and total core lengths) increased ($p<0.001$) and PCa rates decreased ($p<0.001$) steadily with increasing prostate volume categories. PCa percentages decreased in all categories above the utilized cut-offs for mean ($p>0.05$), average ($p<0.05$), and total core lengths ($p>0.05$).

Conclusion: There was no difference between mean core lengths of benign and malignant cores. Total core length and average core length were not significantly associated with PCa. Contrary to the cut-offs used for mean and average core lengths in the published studies, PCa rates decrease as these core lengths increase. Larger studies are necessary for the determination and acceptance of accurate cut-offs.

Keywords: Core length; prostate biopsy; prostate cancer; prostate volume; transrectal ultrasound.

Introduction

Only a few papers in the literature have aimed to evaluate the improvement of the quality of prostate biopsies with sophisticated parameters like biopsy core length (CL) for the detection of prostate cancer (PCa).^[1-3] Different guidelines have recommended a minimum 10 mm CL cut-off value for adequate prostate biopsy.^[4-6] Additionally, longer biopsy CL cut-offs of 11.9 mm^[2] and 13 mm^[3] were also dictated by two other studies. But these two studies have some unclear and problematic aspects. On the

other hand, studies have evaluated the biopsy CLs with different approaches. Iczkowski et al.^[1] compared the total sum of each patients' CLs, Obek et al.^[2] compared average CLs (total sum of CLs divided by total number of samples-ACL) in each patient, and Fiset et al.^[3] compared mean CLs (MCL) of pooled benign and malignant cores. In this study, we aimed to determine whether PCa detection is affected from CLs according to all of these three different approaches in our larger standard biopsy cohort, and compare with the published cut-offs.

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Material and methods

Between March 2009 and March 2014, a total of 1,712 consecutive initial transrectal ultrasound (TRUS)- guided prostate biopsies performed in a single center, all from different patients, were retrospectively evaluated. Systematic 12- core biopsies (from lateral and medial sagittal plane of the peripheral zone at the base, mid and apex of the prostate on the right and left sides) were homogeneously performed for all prostate volumes (PV), ages or total PSA (tPSA) levels (Figure 1). Extra biopsies were also obtained from hypo-echoic areas whenever it is deemed necessary. No transitional zone, and finger guided biopsies were performed. Patients age, tPSA values before biopsy, calculated PV (with the ellipse method: length X depth X width X $\pi/6$) using TRUS, digital rectal examination (DRE) results and CLs in each biopsy were noted.

Benign prostatic pathologies, low and high grade prostatic intraepithelial neoplasia and atypical small acinary proliferations were categorized as non-cancer (benign), and prostate adenocarcinomas were categorized as cancer (malignant). Any individual core (not the patient) without prostatic glandular tissue was excluded before the analysis. DRE is categorized as negative (benign) and positive (suspicious).

For standardization, cancer diagnosis other than prostate adenocarcinoma (n=4), with total number of evaluable glandular cores <8 (n=93), at least one core in the biopsy set with more than two fragments (n=16), incorrectly numbered or dried biopsies (n=4), and patients who previously had 5-alpha reductase inhibitory treatment (n=72) were excluded from the study. Remaining 1,523 patients were included in the analyses.

The PVs were categorized into four groups (<30, 30-59.99, 60-119.99, and ≥ 120 cm³). Biopsies were categorized as benign and malignant and compared with respect to total CL (TCL), ACL, and MCL. TCL is the sum of the lengths of cores obtained from each patient. ACL was calculated for each patient separately and TCL divided by the total number of cores. MCL is defined as the mean of the sum of the lengths of all cores (n=17,074) of the whole cohort pooled together. In other words, MCL is calculated by dividing the total length of the all cores in the whole cohort pooled together by the total number of cores (n=17,074). MCL is also calculated separately for benign (n=13,853) and malignant (n=3,221) cores. These definitions are identical with those in the published literature.^[1-3] TCL (<120.0 and ≥ 120.0 mm). ACL (<10.0 and ≥ 10.0 , <11.9 and ≥ 11.9 mm) and MCL (<10.0 and ≥ 10.0 , <13.0 and ≥ 13.0 mm) were categorized according to the recommended cut-off values indicated in the guidelines^[4-6] and the cut-offs (11.9 for ACL and 13.0 for MCL) published in the relevant manuscripts.^[2,3]

Figure 1. Biopsy scheme

Prostate biopsies were performed by last year urology residents under the coordination of a senior author (OD). Biopsies were separately placed on an absorbent paper and stored in the Eppendorf tubes. Upon arrival at the pathology department each core was measured before it was embedded in paraffin. All biopsies were evaluated by the same expert pathologist (BM).

Statistical analysis

All data was analyzed with Statistical Package for Social Science (IBM SPSS Statistics; Armonk, NY, USA) version 21.0 database program. The Independent Sample-t, and Mann-Whitney U and Chi-square tests were used for parametric and non-parametric analyses, respectively. Spearman's test was used for correlations. Univariate and multivariate logistic regression (LR) analyses were done. One-factor ANOVA was used to test the effect of the PV categories on the TCL, ACL, and MCL values. The robust tests equality of means (Welch, Brown- Forsythe) were used and the linear trend was tested by the polynomial contrast analyses. A p<0.05 was considered to be statistically significant.

Results

In the whole cohort, median patient age, PV and tPSA were 66 years [interquartile range (IQR) 60-72], 46.50 cm³ (IQR 32.40-69.60), and 8.30 ng/mL (IQR 5.62-14.40), respectively. PCa was found in 41.5% (633/1,523) of the patients. DRE was positive in 945 (62.0%), negative in 546 (35.9%), and it was not indicated in 32 (2.1%) men. The mean TCL and ACL values were 117.86 $\pm$ 31.51 and 10.44 $\pm$ 2.36 mm, respectively. The MCL (all cores pooled) was 10.51 $\pm$ 4.33 mm. PCa was detected in 18.9% of all pooled cores. There was no significant (p=0.768) difference between MCLs of benign (10.51 $\pm$ 4.37 mm) and malignant (10.49 $\pm$ 4.18 mm) cores.

Characteristics of cores according to benign and malignant categories are summarized in Table 1. The patients with PCa were

Table 1. Patient characteristics

	Benign	Malignant	p
n (%)	890 (58.5)	633 (41.5)	
Age (yr), median (IQR)	65 (58-70)	68 (62-75)	<0.001
tPSA ng/mL, median (IQR)	7.15 (5.28-11.08)	10.44 (6.10-24.80)	<0.001
PV cc, median (IQR)	51.30 (36.60-75.60)	40.20 (28.85-59.00)	<0.001
Total number of cores, median (IQR)	11.00 (11.00-12.00)	11.00 (10.00-12.00)	0.202
Total core length (mm), mean±SD	119.80±30.77	115.13±32.35	0.004
Average core length (mm), mean±SD	10.59±2.34	10.23±2.38	0.003

IQR: Interquartile range; SD: standard deviation

Table 2. Univariate and multivariate logistic regression (LR) analyses according to the presence of prostate cancer

		OR (95% CI)	p
Univariate LR	TCL	0.995 (0.992-0.999)	0.004
	ACL	0.937 (0.897-0.979)	0.003
	LogPV	0.141 (0.088-0.228)	<0.001
	DRE	3.523 (2.826-4.393)	<0.001
	LogPSA	5.277 (3.925-7.094)	<0.001
	Age	1.054 (1.041-1.068)	<0.001
Multivariate LR*	TCL	0.997 (0.993-1.001)	0.190
	LogPV	0.055 (0.027-0.111)	<0.001
	DRE	2.068 (1.581-2.705)	<0.001
	LogPSA	5.308 (3.742-7.532)	<0.001
	Age	1.045 (1.028-1.061)	<0.001
	ACL	0.959 (0.908-1.013)	0.133
	LogPV	0.055 (0.027-0.109)	<0.001
	DRE	2.062 (1.577-2.697)	<0.001
	LogPSA	5.304 (3.738-7.525)	<0.001
	Age	1.045 (1.028-1.062)	<0.001

LogPV: Logarithms of prostate volume; LogPSA: Logarithms of tPSA; MCL: mean core length; ACL: average core length; TCL: total core length; DRE: digital rectal examination

*TCL and ACL are similar parameters that are derivatives of each other. Therefore, multivariate LR run separately. However, did not make any change when they run together.

significantly older, and had higher tPSA and lower PV values than BPH patients (Table 1). The mean TCL and ACL were also significantly higher in benign patients ($p<0.05$).

Univariate and multivariate LR analyses according to the presence of PCa (dependent variable) are given in Table 2. Lower

LogPV, positive DRE, higher LogPSA, and older age were significant predictive factors both in univariate and multivariate analyses. Although significant (inverse significance), the ORs of TCL and ACL were very close to 1.00 in univariate LR analysis. Therefore, TCL and ACL lost their significance slightly in multivariate LR analysis ($p=1.90$, $p=0.133$, respectively).

The percentage of PCa, the MCL values, and the mean values of ACL and TCL according to increasing PV categories are given in Table 3. The percentage of PCa decreased as PV categories increased ($p<0.001$). There was a significant direct relation between PV categories in MCL ($p<0.001$), ACL ($p<0.001$), and TCL ($p<0.001$). Also, MCL, ACL and TCL increased steadily with increasing PV categories, resulting in a significant linear trend for MCL ($p<0.001$), ACL ($p<0.001$), and TCL ($p<0.001$). In the correlation analyses; MCL, ACL, and TCL had significant positive correlation with PV ($r=0.090$, $p<0.001$; $r=0.170$, $p<0.001$; $r=0.198$, and $p<0.001$, respectively).

The percentage of PCa values according to different cut-off categories of MCL (<10.0 and ≥ 10.0 , <13.0 and ≥ 13.0 mm), ACL (<10.0 and ≥ 10.0 , <11.9 and ≥ 11.9 mm) and TCL (<120.0 and ≥ 120.0) are given in Table 4. Although the difference was significant in only ACL, the PCa percentages decreased in all categories above the utilized cut-offs for MCL, ACL, and TCL.

Discussion

We uniformly performed systematic 12 -core biopsies for all PV, age or tPSA levels. Remzi et al.^[7] suggested a Vienna Nomogram (VN) protocol where the optimal core number in biopsies ranged between 6 and 18 cores according to age and prostate volume (greater number of cores in younger patients and larger prostates vs. smaller number of cores in older patients and smaller prostates). However, Lecuona et al.^[8] reported no significant advantage of VN compared with their 8-core biopsy protocol. Similarly, Teo et al.^[9] from Singapore also did not find any additional advantage for PCa detection with the use of the VN, and they concluded that their PCa detection rate was only comparable to previously published data for Asian patients (14.9%). Also, EAU prostate cancer guideline did not recommend an initial TRUS-guided prostate biopsy with >12 cores.^[10]

Biopsy core quality is determined by parameters like length of core, amount of actual prostatic glandular tissue as opposed to extraprostatic connective tissue, the presence of glandular tissue, and the degree of fragmentation.^[6,11] Surprisingly, there is only a few studies in the literature aimed to determine the impact of CL on PCa diagnosis.

Table 3. The percentage of prostate cancer, and the mean values of MCL, ACL and TCL according to increasing prostate volume categories

Prostate Volume (cm ³)	n	PCa, n (%)	MCL (mm) (mean±SD)	ACL (mm) (mean±SD)	TCL (mm) (mean±SD)
<30	314	176 (56.1)	9.89±4.09	9.83±2.10	107.85±28.68
30-59.99	718	309 (43)	10.51±4.38	10.45±2.44	117.93±31.91
60-119.99	445	138 (31)	10.87±4.38	10.80±2.36	123.80±31.52
≥120	46	10 (21.7)	11.08±4.19	11.07±2.12	127.48±26.41

MCL: mean core length; ACL: average core length; TCL: total core length; SD: standard deviation; PCa: prostate cancer

Current literature includes data for and against the significant impact of biopsy CL on the detection of PCa. Among those against the positive impact of CL was the study of Iczkowski et al.^[11] where they evaluated the impact of the biopsy CL for the detection of PCa. They assessed consecutive sextant (not 12 cores) prostate biopsies from two different centers (Pennsylvania and Virginia). They did not find any significant difference in TCLs between benign and malignant patients. Additionally, when they used needles for longer core grooves (25 mm vs. 20 mm), they obtained longer biopsy cores. However, these longer cores did not detect more cancer. Similarly, although Ficarra et al.^[12] did not give data for TCL, they compared mean lengths of the benign and malignant biopsy cores from 14 separate sites in their perineal prostate biopsy cohort, and did not find any significant difference. Recently, Lee et al.^[13] published the analyses of their data on 3,479 patients who had had ≥12- core TRUS-guided prostate biopsies. They found no significant difference between patients with PCa and without PCa regarding mean CL. Furthermore, they found that CL did not affect PCa detection in multivariate analyses.

Literature in favor of the positive impact of CL is mainly based on two studies that suggested a biopsy CL cut-off value for PCa detection.^[12,3] However, these cut-offs can be questioned related to some unclear and problematic aspects in their manuscripts. Besides, suggested cut-offs were obtained by different methods. Obek et al.^[2] compared ACLs between benign (n=171) and malignant (n=74) patients, and suggested that 11.9 mm should be a minimum cut-off value for detection of PCa. Although they claimed that this cut-off had optimal sensitivity and specificity, we could not find the exact values. Additionally, they excluded less than 12- cores in their biopsies obtained according to slightly modified VN (exact biopsy method unclear).^[7] In this condition, they might have excluded some patients with PVs less than 40 cc and this most probably leads to a selection bias for larger prostates, and longer cores according to the results of our study. On the other hand, Fiset et al.^[3] evaluated 85 malignant and 112 benign patients. When they pooled 2,196 cores into benign and malignant groups they found a MCL of 13 mm as a cut-off value with optimal sensitivity and specificity (76.5% and 42.8%, respectively). However, against their claims of optimal

Table 4. The percentage of prostate cancer according to different cut-off values for MCL, ACL and TCL

	Benign	Malignant	p
Mean core length (mm)	<10.00	19.2 (1281/6673)	0.375
	≥10.00	18.7 (1940/10401)	
Mean core length (mm)	<13.00	19.1 (2266/11886)	0.313
	≥13.00	18.4 (955/5188)	
Average core length (mm)	<10.00	44.5 (286/643)	0.048
	≥10.00	39.4 (347/880)	
Average core length (mm)	<11.90	43.4 (490/1128)	0.012
	≥11.90	36.2 (143/395)	
Total core length (mm)	<120.00	43.4 (340/784)	0.141
	≥120.00	39.6 (293/739)	

MCL: mean core length; ACL: average core length; TCL: total core length

sensitivity, and specificity their false positive rate was very high (57.2%). Additionally, we think that their ROC curve is too undulated and close to 0.5 which also lacks statistical power to determine a cut-off value.^[13]

If prostate could be adequately sampled, the CL might have a minimal impact on the detection of PCa. In the current study, our MCL is concordant with the guideline recommendations (10.51±4.33).^[4-6] Additionally, we found PCa in 41.5% of the patients which is compatible with the literature.^[14-17] However, TCL and ACL were not significantly associated with PCa in our multivariate analysis. Furthermore, when we pooled all cores, we found no significant difference among cores regarding MCL. There may be some explanations for the insignificant difference in our studied parameters. First, prostate biopsies are performed in a systematic manner. In this situation, if a core misses a cancer, it can be hit by adjacent core. Furthermore, due to the localization of different cancer loci, longer cores may miss cancer, while a short core can hit it.

Second, longer cores may be theoretically better in sampling cancers that lay deep in the gland. Men with larger prostates

generally have higher PSA values, with less PCa, but they are more likely to undergo biopsy because of high tPSA. Additionally, benign prostatic hyperplasia (BPH) is mostly responsible for significant increase in overall prostate size. It has been very well demonstrated previously that greater PV was associated with decreased risk of PCa.^[17-19] We also found that all biopsy CLs (TCL, ACL, and MCL) were positively correlated with PV. Similarly, Lee et al.^[13] found a significant positive correlation between their CL (no description given) and PV. Additionally, we found that percentage of PCa decreased and all studied parameters (MCL, ACL, and TCL) increased steadily with increasing PV categories in our study.

We further analyzed the impact of the increasing MCL, ACL and TCL categories on PCa rates. We found an obvious decreasing trend in PCa rates in all increasing categories, opposite to the published studies that utilized identical cut-offs.^[2,3] This is most probably because, PCa rates decrease and CLs increase as PV increases. Consequently, these findings suggest that longer biopsies are not a prerequisite for increased PCa detection in initial prostate biopsies. On the other hand, it is difficult to estimate the diagnostic accuracy of a biopsy for PCa, because all men with negative biopsies do not undergo radical prostatectomy and thus all biopsy findings can not be confirmed precisely.

It has been proposed that longer biopsies would detect greater number of PCa. However, there is no consensus for minimum cut-off value of CL in the literature. A minimum 10 mm CL is recommended in the Italian guideline^[5] and 2013 guideline on processing and reporting of prostate biopsies^[5] based mainly on expert opinions rather than sound data. European Association of Urology Prostate Ca Guideline states that the length of biopsy tissue significantly correlates with the PCa detection rate.^[10] However, our data in the current study could not allow determination of a cut-off value, because benign and malignant CLs were not significantly different. Our study also showed that longer CL is associated with larger prostates, and lower rates of malignancy, most probably because BPH predominates in larger prostates. This is also true when guideline cut-off (10 mm) value and cut-off values in the reference studies (13.0 mm for MCL and 11.9 mm for ACL) are used. So, based on this study it seems not reasonable to recommend additional biopsy and the related risks for every biopsy that is shorter than 10 mm for the detection of PCa. On the other hand, based on our previous study^[20] minimum CL of 6 mm should be kept in mind for the presence of prostatic glandular tissue in the biopsy.

This study has some limitations. Subjects were tested during a relatively longer period of time in a retrospective study. Additionally, the biopsy CL was evaluated regarding only the presence of PCa, not with other prognostic parameters. There

are also some advantages of this study. Our study has higher number of patients and all of the biopsies were obtained in the same manner with sound data.

In conclusion, TCL and ACL are not significantly associated with PCa in multivariate analyses. Furthermore, there was also no significant difference between MCLs of benign and malignant cores. As CLs increased, PCa detection rates decreased significantly with increasing PV categories. On the other hand, contrary to the cut-offs used for MCL and ACL in the published studies and in the guidelines, detection rates of PCa decrease when core lengths above these cut-off values were obtained. Therefore, these cut-off values were not verified in our data. For this reason, it is not reasonable to recommend additional biopsy for every biopsy core length that is shorter than 10 mm for the detection of PCa. Because the issue became further controversial with the data in this current study, additional larger studies are seriously required.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”, (amended in October 2013).

Informed Consent: This article is based on a retrospective study. All data were collected from the hospital record system.

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