Length of prostate biopsy cores: does it impact cancer detection?

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Introduction: *The detection of prostate carcinoma relies on adequate sampling. We aimed to evaluate whether core length is a significant biopsy parameter in the detection of cancer, especially in the low risk cancer category group.*

Materials and methods: *We retrospectively analyzed pathology reports of 197 patients (2196 biopsy cores) undergoing initial transrectal ultrasound guided biopsy. A multivariate analysis of age, total prostate-specific antigen (PSA) concentration, prostate gland volume, total number of cores and length of biopsy cores was performed. Secondary analyses included stratification by Gleason score. Single core analysis was done to calculate a workable cut off value for core length with optimal sensitivity and specificity in carcinoma detection.*

Results: *Mean age, PSA, prostate volume, and total number of cores were 66.9 years, 12.6 ng/mL, 47.2 cc and 11.1 cores, respectively. Whereas detection of cancer was significantly associated with advanced age ($p < 0.01$) and smaller prostate volumes ($p < 0.001$), PSA levels ($p = 0.40$) and number of cores ($p = 0.20$) were not significant predictive factors. Assessment of biopsy core lengths showed that cores harboring cancer ($n = 307$, average length 14.1 mm) were significantly longer than benign cores ($n = 1889$, average length = 13.2 mm) ($p < 0.001$). Core length analysis yielded 13 mm cores have an optimal sensitivity (42.8%) and specificity (76.5%) for detection of carcinoma (odds ratio: 2.43). Secondary analyses of Gleason score did not show any difference with respect to core length.*

Conclusion: *This study suggests that core length is a biopsy parameter that affects detection of cancer and is an essential parameter for core biopsy quality.*

Key Words: carcinoma, prostate, biopsy, core length, detection

Introduction

Currently the deciding factors to undergo prostatic needle biopsies include abnormal digital rectal examination (DRE) and either absolute prostate-specific antigen (PSA) concentrations or PSA-related parameters. A patient undergoes a set of first biopsies and the pathologic findings will dictate if the patient undergoes repeat biopsies. Optimizing the success of finding prostate cancer when it is present in the first set of biopsies or during active surveillance therefore reduces the time-to therapy. Historically, the diagnosis of prostate cancer was performed by DRE and digitally directed biopsy. Systematic sextant biopsies combined with ultrasound guidance was shown to be superior to digitally directed biopsy.[1] Currently, most first biopsy protocols recommend the traditional sextant scheme with sampling of the lateral peripheral zone (the extended prostate biopsy scheme), for a total of 10-12 cores; the majority of urologic societies currently

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consider this protocol as the standard of care.[2] This has proven to be superior in terms of cancer detection both in population-based and autopsy-based studies.[2,3] For example, using the extended biopsy scheme in prostates derived from autopsies yielded a sensitivity of 80% for clinically significant cancers compared to the 30% sensitivity of sextant biopsies.[4] During the development of the traditional sextant biopsy and extended prostate biopsy scheme, much of the focus has been placed on increasing core numbers and core location to increase detection rates. Increasing the number of cores essentially increases the amount of tissue available for histopathologic evaluation. However, other parameters that can increase the amount of tissue analyzed include increasing core volumes with larger bore needles, and also increasing biopsy core length. Longer cores may be theoretically better at sampling cancers that are found deeper within the gland especially in large prostates. Although few studies have looked at core length as a potential variable for optimizing prostate core biopsy, only one has done so using the extended prostate biopsy scheme, and this was performed in a limited clinical setting.[5-9]

In this study, our primary aim was to determine if biopsy core length is a determining factor in the detection of prostate cancer independently from other clinical parameters such age, PSA concentration, and prostate volume and within the context of modern extended biopsy technique. We retrospectively analyzed the biopsy cores sent from multiple urologists to our hospital network pathology department, which provides an accurate representation of actual clinical settings. We also aimed to provide a workable standard cut off that can help clinicians in assessing the adequacy of sampling extent when interpreting the final pathology report.

Materials and methods

Patient selection

Using the Laboratory Information System (LIS) of the McGill University Health Center hospital network, prostate biopsy reports were obtained for patients between January 2011 and December 2011. The network includes two major hospital centers in Montreal with prostate cores obtained from several physicians. We obtained biopsy reports for 359 patients. Patients underwent a first set of biopsies based on abnormal digital rectal examination and PSA of greater than 4.0 ng/mL and underwent repeat biopsies as part of active surveillance for persistently abnormal PSA parameters, abnormal imaging or DRE, and previous diagnoses of high grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation of prostate (ASAP). Our database was created from this data including patient demographics, number of cores, length of prostate cores and individual diagnosis for each core and overall diagnosis for each patient. PSA levels and prostate volumes were obtained by separate searches of the LIS. Prostate biopsies were all obtained by transrectal ultrasonography (TRUS)-guided biopsies with the patient in the lateral decubitus position with either periprostatic nerve block, or under procedural sedation and analgesia with midazolam and remifentanil. Volumes of the prostates were measured using TRUS. Biopsies were obtained using the traditional sextant biopsy scheme with lateral extensions for a total of 8 to 16 cores per patient, depending on the prostate volume. Prostate cores were removed using an 18-gauge biopsy-gun and placed into individual specimen containers containing 4% phosphate-buffered formaldehyde solution. Once in the pathology department, individual cores were measured with a ruler. The cores were then transferred to processing cassettes, underwent paraffinization, and were sectioned at 4 µm for deparaffinization and routine hematoxylin and eosin staining. Microscopic slides were analyzed by three pathologists (one uropathologist and two pathologists with genito-urinary pathology experience) within the department. The length of the prostate cores as well as the percent of the cores involved by cancer was recorded in the pathology department report. Diagnoses provided by the pathology reports were recorded and slides were not reviewed for the purpose of the study. Only first-biopsy patients were included in this study (n = 253). Patients were excluded if they had a prior diagnosis of prostate cancer or previous anti-androgen or radiation therapy. Patient data was also excluded if cores were submitted to the pathology department in multiple fragments (> 2 fragments) as this prevents accurate millimetric core measurement (n = 56). Cores with diagnoses of either HGPIN and ASAP were grouped with the benign category. Cores that contained rectal mucosa or periprostatic tissue only and not prostatic stroma or glands were also excluded.

Statistical analysis

Primary analysis and calculation of odds ratio (OR) and 95% confidence intervals (CI) were performed with a univariate and multivariate analysis of the data, using a general linear model. A secondary analysis was performed by stratification of the patient cores by Gleason Score (GS) and also by percent length of the core involved by cancer using cumulative logit

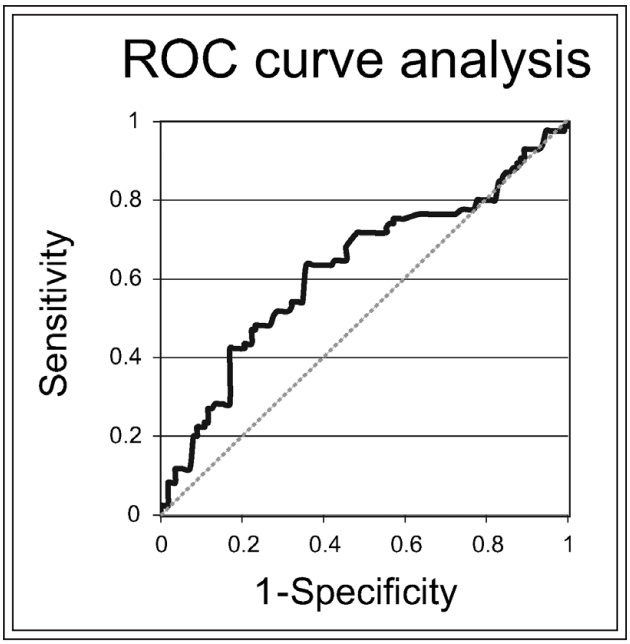

Figure 1. ROC curve for core lengths. The detection of cancer for individual core lengths were compared to set cut-off values and sensitivity and specificity were obtained from each and plotted to form the ROC curve (solid black line). The dotted line shows the line of no discrimination. (C = 0.63; p = 0.016).

mixed model. By using the overall diagnosis in patient of carcinoma or no carcinoma, the cores were separated according to their true positive rate and false positive rates. True positive rates (TPR) and false positive rates (FPR) were determined by comparing how often a cores did or did not show cancer when compared to set cut off values (from 5 mm-20 mm) for the core length. The TPR (sensitivity) and the FPR (1-specificity) were used to plot a receiver operating characteristic (ROC) curve as shown in Figure 1. The Concordance (C) statistic was calculated from the area under the ROC curve and measures how accurate length can be used as a variable to discriminate cores with or without cancer. Sensitivity and specificity were also used to calculate the odds ratio (OR). Statistical Analysis System software (SAS, version 9.2) was used to perform the statistical analysis. All tests were 2-sided with significance at $p \leq 0.05$. The type 1 error was not adjusted for multiple comparisons.

Results

Biopsy samples from 359 patients were evaluated. Fifty-six patients were excluded because at least one of their cores in their biopsy set had more than two fragments. One hundred six patients were excluded because of a previous biopsy or diagnosis of prostate cancer. Thus, after exclusion we evaluated the core biopsies of 197 patients, which constituted 2196 individual biopsy cores. The mean age was 66.9 ± 8.4 years, the mean total PSA was 12.6 ± 37.0 ng/mL and mean prostate volume was 47.2 ± 22.4 cc. The mean number of core biopsies per patient was 11.1 ± 2.0 cores and the overall mean length of the cores was 13.1 ± 2.0 mm. Individual core lengths ranged from 1.0 mm to 31.0 mm where 95% of cores ranged between 7.0 mm and 18.0 mm with a variation of 2.6 fold. The overall cancer detection rate was 43.1% with 85 patients given a diagnosis of prostate adenocarcinoma and 112 patients with benign cores. Isolated HGPIN or ASAP, which were grouped with the benign cores' category were seen in 35 (17.8%) patients. Of the 85 patients with adenocarcinoma and considering the highest GS among all cores as the final GS, 46 patients had GS of 6, 26 patients had GS7, and 13 patients had GS ≥ 8. The mean number of cores with prostate carcinoma per patient was 1.59 ± 2.6 cores.

Univariate analysis of patients given a diagnosis of prostate adenocarcinoma versus those given a benign diagnosis was performed, Table 1. Age, prostatic volume

TABLE 1. **Univariate analysis of patient cores**

Characteristic	**Cancer Mean ± Std Dev. (n)**	**No cancer Mean ± Std Dev. (n)**	**Odds ratio (95% confidence intervals)**	**p value**
Age	69.0 ± 8.4 (85)	65.2 ± 8.1 (112)	1.06 (1.02-1.10)	0.002
PSA (ng/mL)	15.0 ± 29.5 (84)	10.7 ± 42.0 (107)	1.00 (1.00-1.01)	0.454
Volume by ultrasound (cc)	40.3 ± 18.8 (69)	52.3 ± 23.5 (93)	0.97 (0.95-0.99)	0.001
Total number of cores	11.2 ± 2.16 (85)	11.1 ± 1.9 (112)	1.01 (0.88-1.16)	0.914
Length of cores	14.1 ± 2.2 (85)	13.3 ± 1.8 (112)	1.20 (1.04-1.40)	0.016

TABLE 2. **Multivariate analysis of patient cores**

Characteristic	Odds ratio (95% confidence intervals)	p value
Age	1.06 (1.01-1.10)	0.014
PSA (ng/mL)	1.00 (1.00-1.01)	0.333
Volume by ultrasound (cc)	0.97 (0.95-0.99)	0.001
Total number of cores	1.01 (0.51-1.12)	0.159
Length of cores	1.30 (1.08-1.57)	0.005

and core's length were significant in the univariate analysis, while PSA and the total number of cores did not. These differences were maintained in the multivariate analysis of the data, Table 2. Older age was associated with a higher odds ratio for carcinoma detection (OR = 1.06, 95% CI, 1.01-1.10, p = 0.014). Volume analysis showed that smaller prostate volumes were associated with cancer in our cohort in the multivariate analysis (OR = 0.97, 95% CI, 0.95-0.99, p = 0.001). Longer length of prostate core biopsy was associated with the highest odds ratio (OR = 1.30, 95% CI, 1.08-1.57, p = 0.005). PSA and the total number of cores were not significant in the multivariate analysis.

In order to evaluate whether detection of high grade cancer component was affected by cores' lengths, a secondary analysis was performed by stratifying patients diagnosed with cancer based by on the final GS (GS of 6, 7, ≥ 8). No difference was seen in univariate analysis for age (p = 0.46), volume (p = 0.25), PSA (p = 0.36), core length (p = 0.12) or number of cores (p = 0.41).

In addition to analyzing the data per-patient, we used individual core length of the 2196 included cores to confirm our findings. Sensitivity and specificity were obtained by comparing individual core lengths to set cut off values, and a ROC curve was constructed for the length variable, Figure 1. From the ROC curve a significantly statistical concordance was found between the detection of cancer and a set cut off value for core length (C = 0.63; p = 0.016). From this model, a 13 mm length cut off showed optimal sensitivity (76.5%) and specificity (42.8%) for cancer detection.

Discussion

Prostate cancer remains the most common non-skin related cancer in men. Despite efforts made to identify new serum and biologic markers of disease and refinement of imaging modalities, the diagnosis of prostate cancer still relies on biopsy procurement for histopathologic analysis. Accurate prostate core analysis, itself, relies on biopsy site and appropriate sampling of prostatic tissue. In the past years much emphasis has been placed on the number and location of the cores, but the quality of the biopsied tissue is also important for the diagnosis and has not been fully evaluated previously. Few reports exist on the importance of biopsy core length for an accurate diagnosis of prostate cancer.[5-9] Although it is a recommended biopsy parameter recorded to include in a pathology report,[5,10] length of cores was regarded as one of the lesser important parameters in previous surveys of both the members of the Society of Urologic Oncology and the French Association of Urologists.[11,12] Our results confirm, in a multivariate analysis, that prostate core length can be considered a key determinant in the detection of cancer. In addition to an abnormal DRE, current guidelines utilize PSA levels or change in its levels to screen for prostate cancer and select patients for initial prostate biopsies.[2] In the era of PSA screening smaller cancers are detected, smaller than can be detected by DRE or difficult to discern by current imaging techniques. With these limitations, systematic sampling of the prostate is performed, usually with 10-12 core biopsy TRUS-guided schemes. This includes the traditional sextant template with a lateral sampling. Some protocols, such as the Vienna nomogram, uses age, PSA and prostate gland size to recommend the minimum initial number of cores, from 8-18.[13] In addition to increasing adverse events, biopsy schemes that use 18-24 cores have not been confirmed to significantly detect more cancer compared to the 12 core scheme.[14] In our cohort, the total number of cores ranged from 8 to 16 cores with a mean of 11.1 cores per patient. Total number of cores was not significant in our analyses, and this is likely because almost all (96%) of our cohort was biopsied using the 10-12 core extended sextant protocol. Regardless of the number of biopsies acquired, to confidently accept a negative diagnosis in a patient, biopsy quality should be optimal.

Few studies have examined the question of the importance of biopsy length in prostate cancer. Iczkowski et al, performed a retrospective analysis of prostate core lengths in two centers in Pennsylvania (251 patients; 1506 biopsy cores) and Virginia (1596 patients; 9576 biopsy cores).[8] They used 18G needle biopsies and included only patients that underwent sextant biopsies. Their overall mean was 12.8 ± 3.5 mm. They found a correlation between prostate core length and the detection of cancer, but this was only significant for biopsies taken at the apex. This may be explained by their having a significantly higher number of shorter

cores in the apex compared to other biopsy sites. In a second outcome analysis, Iczkowski et al subdivided their cores with diagnoses of either benign, ASAP and HGPIN and cancer. They found that longer cores were associated with a diagnosis of ASAP again at the apex. Our primary analysis was to determine the diagnosis of prostate cancer and thus we grouped ASAP and HGPIN with benign cores. We did not perform secondary subgroup analysis as few cores had ASAP or HGPIN as diagnosis and conclusions could harbor statistical error. Similarly, Ficarra et al, analyzed biopsy core lengths during a prospective evaluation of 509 patients (7126 cores) undergoing first set of biopsies, taken by transperineal approach using a 18G needle with a coaxial needle as a guiding cannula.[6] They used a 14-core topographic scheme that sampled the right and left apices, mid-portion, base and transition zone. However, unlike the extended biopsy scheme, only 2 of their 14 core scheme were of the transition zone. Using these methods, they were able to obtain an overall mean core length of 14.14 ± 4.4 mm and better sampling of the apex (15 ± 2.3 mm and 14 ± 2.1 mm for the right and left apices, respectively). In addition, they excluded patients from their cohort if core lengths were less than 10 mm. Although there was a trend for positive cores to be longer, lengths' ranges significantly overlapped. On the other hand, they obtained much longer mean core lengths compared to our study, denoting that transperineal approach may yield higher quality tissue. Finally, Obek et al also performed a recent analysis of length of prostate biopsies.[9] They performed a retrospective analysis on a cohort of patients (331 patients; 245 patients included in their analysis) from a single center, but with the extended sextant of 12-18 cores. To reduce confounding factors, their protocol involved coordination between a single urologist and nurse, using the same biopsy gun, 18G needles and a single ultrasound machine to perform their biopsy. Overall mean core length was 11.4 ± 2.5 mm and they were able to find that cores harboring cancer were significantly longer than those without (12.3 ± 2.6 versus 11.4 ± 2.4 mm). Our protocol used multiple urologists from two clinics in our hospital network. This may have introduced confounding factors into the study due to the less controlled clinical setting. Unlike Obek et al, we performed a multivariate analysis to examine dependencies between clinical and biopsy parameters; core length was reproducibly and independently associated with the detection of cancer. Despite the more rigid protocol followed by Obek et al, they encountered a significant range of biopsies ranging from 4.5 mm to 17.8 mm which would come to a variation of 4.0 fold. This range is comparable to the range observed by Iczkowski et al, which had a 95% range of 5 mm to 18 mm with a variation of 3.6-fold variation.[8] We had a smaller but still noteworthy variation of 2.6 fold. The tremendous variability in the size of the cores may be due to multiple factors at any point in acquisition of the biopsy and preparation for analysis by a pathologist. The needle takes an imprecise path to get to the prostate and occasionally, the prostate gland may be missed. This results in biopsies of either bowel wall or connective tissue around the prostate. Patient body habitus or an enlarged or abnormally shaped prostate may increase the difficulty of the procedure. Sampling the apex of the prostate is often problematic and results in shorter cores.[8] The size of the needle and the type of needle or biopsy gun may impact on specimen quality.[15] Biopsies may also fragment during the biopsy procedure and manipulations prior to fixation, during tissue processing, and embedding. Indeed, we excluded 56 patients from our cohort due to fragmentation. At least 11% of our cohort of cores had lengths less than 10 mm, which may be explained by fragmentation and loss of tissue prior to tissue processing. Fragmentation is a known issue in prostate core biopsy processing and is associated with needle core length, submission of multiple cores together in the same container, and a higher Gleason score.[16] Given the multiple steps involved, standardization and efficient handling is essential for high quality biopsy analysis. In a recent worldwide study on biopsy needle quality, Bostwick et al, variance can be reduced by urologist training and standardization of collection and processing.[17] They collected data from 4649 subjects at entry and 6267 subjects at year 2 in six geographic regions from more than 800 sites worldwide. Initial biopsy mean lengths ranged between 9.4 mm to 15.1 mm, but after investigators received biopsy guidance manuals and video training, the lengths significantly increased to a range between 16.1 mm to 17.4 mm. However, they did not analyze whether there was increased detection of cancer associated with longer core lengths.

It has been recommended by Boccon-Gibod et al and the pathology committee of the European Randomized Study of Screening for Prostate Cancer that core lengths should be > 10 mm to be of adequate quality for histopathologic analysis.[5,10] Based on our analysis this would yield a sensitivity of only 6.2% but a specificity of 97.7% at predicting cancer. This implies that at this threshold there would be a substantial level of 'false negative' results, at the detriment of the patient, who would likely be re-biopsied. We confirm, as was seen by Obek et al, that the detection of cancer may benefit by increasing the threshold for core lengths, or at least by decreasing the variability of

cores submitted for analysis. In our hands, a threshold of 13 mm as offered an optimal sensitivity of 42.8%, and specificity of 76.5% (OR 2.43). In our analysis, it offered one of the highest sensitivity and specificity, while still being a measurable value that can be used conveniently in the laboratory or clinic. Of the other variables we analyzed age and prostate volume were significant independent factors. Increased age is a well-known to be associated with the risk of prostate cancer and is an often considered factor considered in indications for initial prostate biopsies.[2] We also found that prostate volume should be negatively associated with a diagnosis of cancer. This may be due to sampling errors that occur in larger prostates, cancer may cause retraction of the prostatic tissue or enlarged prostates contain gland hyperplasia rather than carcinoma. This relationship is known and is sometimes factored in biopsy protocols.[2,13] PSA was not found to be an independent risk factor in our analysis. We did not examine whether PSA density or PSA velocity were better independent factors in our analysis. It is noted however that the average PSA values in the current cohort is actually high (mean =12.6 ng/mL) when compared to the rate of cancer detection. This could be due to the fact that all the included cases represent first biopsies and that no repeat biopsy results were taken into account. Therefore it is conceivable that some of the included negative biopsies are probably false negative which gives an artificial impression of discrepancy between PSA levels and cancer detection rates. We also did not examine the detection rates on repeat biopsy of patients with persistent or increasing PSA levels, where it is known that one-half to one-third of patients could be found to have cancer.[2] Our analysis was based on first biopsy patient only; however future studies correlating repeat biopsy lengths with prostate cancer remain to be done. Whereas a cut off value for what constitutes an adequate biopsy size should be established remains to be seen, however, an easy step to ensure adequate sampling would be for urologists to routinely verify the length of tissue obtained from each biopsy and to re-sample the targeted zone if the cores are too short (i,e. less than 5 mm).

Conclusions

Our findings show that more emphasis should be placed on the prostate biopsy core length to ensure high quality biopsies. Therefore, when interpreting the results of a prostate biopsy pathology report, especially a negative one, urologists should take into consideration core lengths as an important quality parameter influencing cancer detection. □

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