Urologist's Impact on Needle Core Prostate Biopsy Histopathologic Variables Within a Single Institution

Kashika G. Goyal, Joshua J. Ebel, Soud A. Sediqe, David S. Sharp, and Debra L. Zynger

OBJECTIVE To assess the urologist's impact on prostate needle core biopsy variables including number of containers submitted, total core length, longest core length, and individual core length threshold values, and to elucidate the relationship between these variables and cancer detection rate within a recent cohort.

METHODS A retrospective search was performed to identify patients who had an extended transrectal ultrasound-guided prostate needle core biopsy between 2008 and 2013.

RESULTS One thousand one prostate biopsies were analyzed. Total core length (mean 13.2-22.9 cm, $P < .001$) significantly varied by submitting urologist but did not impact cancer detection rate per case. Increased core length per container impacted the cancer detection per container ($P < .001$). The number of cores that met threshold values of 0.5, 1.0, and 1.5 cm as well as longest individual core length (mean 1.7-2.2 cm) significantly varied between urologist ($P < .001$), although there was no association between these variables and cancer detection. Container number differed significantly between urologists ($P < .001$) but did not correlate with cancer detection. For the single urologist with a change in his submission protocol during the study period, a nonsignificant change in cancer detection was noted when comparing 12-14 containers vs 6-9 containers.

CONCLUSION Submitting urologist significantly impacts prostate biopsy metrics. An increased amount of tissue per container was associated with higher rates of cancer per container. A nonsignificant change in cancer detection rate was observed when container number was reduced from 12-14 to 6-9. UROLOGY 92: 70–74, 2016. © 2016 Elsevier Inc.

Despite being used as the gold standard for the detection of prostate cancer, prostate needle core biopsies lack a universally agreed-upon biopsy regimen. The current protocol typically involves extracting 10-12 cores from standard sextant locations.[1-7] Controversy remains regarding the optimal core number and number of containers in which the cores are submitted. Further complicating the matter, the impact of submitting urologist on these variables has not been well assessed.

Past literature suggests that increasing the number of cores per container is associated with increased tissue fragmentation, tangling, and a reduction of the amount of sampled tissue present for histologic examination.[8,9] These observations have led to the recommendation that no more than 2 cores should be placed in a single container.[8,9] Although potentially more information can be gathered by submitting an increased number of cores and separating cores into more containers, this is associated with incurring more cost.[2,10]

Prostate cancer detection has been shown to be increased by sampling more anatomic sites as well as obtaining more cores, but its relation to individual core length, longest core length, and total core length is not clearly understood.[11,12] Previous analyses have proposed minimum core lengths as a quality metric, but the length of a sufficient core remains disputed.[13,14] The purpose of our investigation was to assess the urologist's impact on multiple prostate needle core biopsy variables including number of biopsy containers submitted, total core length, longest core length, and individual core length threshold values, and to elucidate the relationship between these variables and cancer detection rate within a recent cohort of patients undergoing prostate needle core biopsies at a single academic institution.

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From the Department of Pathology, The Ohio State University Medical Center, Columbus, OH; and the Department of Urology, The Ohio State University Medical Center, Columbus, OH

Address correspondence to: Debra L. Zynger, M.D., Departments of Pathology and Urology, The Ohio State University Medical Center, 410 W 10th Ave, E401 Doan Hall, Columbus, OH 43210. E-mail: debra.zynger@osumc.edu

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METHODS

We retrospectively evaluated consecutive men from our academic tertiary care center who underwent a transrectal ultrasound-guided prostate needle core biopsy between July 1, 2008 and June 30, 2013. The study was performed with approval and in compliance with our institutional review board. Cases submitted by urologists with fewer than 100 biopsies and cases diagnosed by pathologists that had fewer than 100 cases were excluded. An 18-gauge biopsy gun was used. Urologists 1 and 2 used end-fire ultrasound probes whereas Urologists 3-5 used side-fire probes. Individual core lengths were measured and recorded at the time of gross examination. Paraffin-embedded tissue was cut into 6 levels placed on 3 slides in which levels 1-2 and 4-5 are stained with hematoxylin and eosin and levels 3 and 6 are saved for immunohistochemistry as needed. The following data were obtained: year of biopsy, patient age, overall case diagnosis, individual container diagnosis, number of biopsy containers (vials) submitted, all individual core lengths, submitting urologist, and case pathologist. Diagnosis per case was recorded (subsequent to immunohistochemical workup that was performed): (1) carcinoma if prostate adenocarcinoma was diagnosed in any container, (2) high-grade prostatic intraepithelial neoplasia (HGPIN) if only HGPIN was found, (3) atypical small acinar proliferation (ASAP) if only an atypical focus of glands was diagnosed in the final report after immunostains were performed, (4) HGPIN/ASAP if both HGPIN and ASAP were stated to be present but no cancer was found, and (5) negative if none of the above were recorded in the pathology report. Diagnosis per container was recorded as (1) carcinoma, (2) HGPIN, (3) ASAP, (4) HGPIN/ASAP, or (5) negative.

Individually measurable tissue cores, including fragments, were recorded if at gross examination they were separately identified and a measurement was documented. Total core length per case was calculated by adding the total tissue amount per container and subsequently adding the total tissue amount in all containers, including all tissue fragments. The longest core length per case and the number of cores per case that met a tissue threshold of 0.5, 1.0, and 1.5 cm were recorded. Urologist 1 submitted 1-2 cores per container, which is a similar submission scheme to that of Urologist 4 later in the time period of the study. Urologists 2, 3, and 4 early in the study submitted 1 core per container. Number of cores submitted per container was not assessed retrospectively due to possible core breakage during the procedure and gross examination. Cases without recorded measurements for every core in every submitted container were omitted from analyses involving total core length per case, longest individual core length per case, and cores meeting threshold for length. Cases submitted in greater than 14 containers and cases from patients who underwent repeat biopsy at our institution during the time of our study were excluded. Cancer detection rate was calculated for each of these parameters, as well as individually for each urologist. In cases in which missing data prevented the overall determination of a parameter, cases were excluded in their entirety. If missing data were associated with the exclusion of a core or container, only those cores or containers were excluded from the analysis.

Urologist 1 had resident involvement in nearly 100% of the cases included in this study, with residents taking all cores. Urologist 2 had resident participation in approximately 90% of cases. Urologists 3 and 4 had resident participation in 50% of cases. Urologists 2-4 routinely had residents sample one side whereas the attending physician sampled the contralateral side. The biopsy template, number of cores taken, number of containers, and the number of sites sampled were determined by the urology attending. All prostate biopsies were submitted within the time period stated, except for a small subset of biopsies that were conducted by Urologist 4 between January 1, 2008 and June 30, 2013. In comparisons between the early and late work of Urologist 4, pathologist was not used as an exclusionary criteria. During this time period, Urologist 4 decreased the number of submitted containers from 12-14 to 6-9 for the sole purpose of reducing patient expenditures, with no other changes to biopsy strategy. As Urologist 4 joined the clinical staff at our academic institution in January 2008, we were limited in the number of cases that could be included in the 12-14 container group and as such no a priori sample size analysis was done.

Statistical analyses were performed using the Kruskal-Wallis one-way analysis of variance test, Pearson's chi-squared test for independence, and logistic regression. The Kruskal-Wallis test was used for comparison of multiple groups of non-normally distributed variables such as with the determination of an overall difference among longest core and total core length among urologists. Chi-squared analysis was used for evaluation of categorical data such as with the difference between rates of cancer in cases with varying container number. Correlations with the binomial variable of cancer presence were assessed by multiple logistic regression controlling for patient age, and pathologist. The level of significance was set at .05. All data analysis was carried out using R version 3.2.2.

RESULTS

Of the 1668 prostate biopsies that were reviewed, 1001 cases met the inclusion criteria for this study (mean age 61 years) (Table 1). Of the 1001 biopsies, 51.5%, 38.9%, 4.7%, 3.4%, and 1.4% were diagnosed as carcinoma, negative, HGPIN, ASAP, and HGPIN/ASAP, respectively. One pathologist completed a genitourinary fellowship (46.1% of cases).

Core Length

The average total core length per case ranged from 13.2 cm to 22.9 cm (Table 2). There were statistically different average total core lengths among urologists ($P < .001$). However, no association was found between the total core length of the prostate biopsy and the cancer detection rate

Table 1. Number and diagnosis of prostate biopsies per urologist. Other denotes a diagnosis of HGPIN, ASAP, or HGPIN/ASAP

	Diagnosis		
	Carcinoma (%)	Negative (%)	Other (%)
Urologist 1 (n = 314)	52.5	39.8	7.6
Urologist 2 (n = 258)	52.3	36.8	10.9
Urologist 3 (n = 184)	43.5	48.4	8.2
Urologist 4 (n = 157)	54.8	33.1	12.1
Urologist 5 (n = 88)	56.7	31.8	11.4
Total (n = 1001)	51.5	38.9	9.6

ASAP, atypical small acinar proliferation; HGPIN, high-grade intraepithelial neoplasia.

Table 2. Average container number, total core length, and average longest core individual length varies significantly per urologist

	Average Container Number	Average Total Core Length (cm)	Average Longest Core Length (cm)
Urologist 1	7.9	13.2	1.8
Urologist 2	11.9	15.3	1.7
Urologist 3	13.9	20.5	2.2
Urologist 4	8.7	18.9	1.9
Urologist 5	12.4	22.9	2.2

per case controlling for patient age, and pathologist ($P = .64$, odds ratio [OR] = 1.0 [0.96-1.02]). There was a significant association between greater total core length per container and cancer detection controlling for age, and pathologist ($P < .001$, OR = 1.25 [1.16-1.34]). Containers with a diagnosis of cancer averaged a total core length per container of 1.71 vs 1.58 cm in containers with a noncancer diagnosis.

Longest individual core length varied significantly among urologists from 1.7 cm to 2.2 cm ($P < .001$). However, there was no association between longest core length and cancer detection rate of the overall case, controlling for age, and pathologist ($P = .30$, OR = 0.88 [0.68-1.12]). Similarly, the number of individual cores that met threshold values of 0.5 ($P < .001$), 1.0 ($P < .001$), and 1.5 cm ($P < .001$) significantly varied between urologists, but there was no association between the number of cores meeting threshold values per case and cancer detection of the overall case ($P = .32$, OR = 1.0 [0.96-1.01], $P = .99$, OR = 1.00 [0.97-1.03], $P = .22$, OR = 1.03 [0.99-1.07], respectively).

Container Number

Significant variation ($P < .001$) was present in the average number of containers submitted by Urologists 1-5 (Table 2). However, no association was found between increasing container number and cancer detection rate per case controlling for age, and pathologist ($P = .01$, OR = 0.94 [0.90-0.99]). Urologist 4 had 2 groups within the study: (1) 12-14 containers early in the study period (n = 57) and (2) 6-9 containers (n = 142) (Table 3). The amount of tissue measured in the 12-14 container group was greater (average total core length 20.1 vs 18.6 cm). The percentage of containers with cancer in the 6-9 container group was 25.2 compared to 18.5 of containers with cancer in the 12-14 container group, an anticipated change due to putting the same number of cores in less containers. Despite decreased measured tissue, the cancer detection rate per case did not change significantly with decreasing the number of containers submitted controlling for age and pathologist ($P = .50$, OR = 1.06 [0.87-1.22]).

Table 3. Prostate core characteristics of the 12-14 vs 6-9 container groups submitted by Urologist 4

	12-14 Containers	6-9 Containers
Total case number	57	142
Average container number	13.7	8.0
Average total core length	20.1 cm	18.6 cm
Average longest core length	2.1 cm	1.9 cm
Percent containers with cancer	18.5	25.2

Comment

Although much emphasis has been placed on exploring the effect of the number of prostate cores obtained on cancer detection, there has been less focus on the impact of the submitting urologist on multiple prostate needle core biopsy variables including number of biopsy containers, total core length, longest core length, and individual core length threshold values.

In our investigation, the submitting urologist significantly impacted prostate biopsy total core length, longest individual core length, and the number of cores meeting threshold values. The average prostate biopsy total core length per case varied from 13.2 cm to 22.9 cm, with an average total core length of 17.1 cm. The average longest individual core per urologist was 1.7 cm-2.2 cm, and 1.9 cm overall. All tissues submitted per case and cases diagnosed as ASAP were included to reflect our clinical practice. One prior publication evaluated the amount of total tissue in prostate biopsies. Iczkowski et al conducted a retrospective analysis of multiple urologists at 2 centers in Pennsylvania and Virginia that utilized a sextant biopsy scheme.[12] In contrast to our study, patients with a previous diagnosis of cancer were excluded, as well as core lengths and diagnoses from sites with more than 1 core submitted, unless the second core was less than 0.3 cm in length. This work demonstrated a difference in prostate biopsy total core length between sites, with an overall mean total core length of 10.8 ± 2.7 cm in the Pennsylvania group vs 8.1 ± 2.2 cm in the Virginia group. Bostwick et al compared biopsy quality factors worldwide prospectively from 4649 subjects through the Reduction by Dutasteride of Prostate Cancer Events Study. This inquiry reported that at time of entry into the study, there were significant differences in aggregate length of cores, mean length of cores, and

number of cores among geographic regions. However, after investigator training, within the follow-up biopsy both total core length and mean core length increased, further reinforcing the impact of the clinician performing the prostate biopsy on quality metrics such as core length and total tissue obtained.[15]

We identified a significant relationship between the total amount of tissue per container and a diagnosis of cancer in that container (1.7 cm in containers with cancer vs 1.6 cm in containers with a noncancer diagnosis). Our data did not demonstrate a significant association between total core length, longest core length, number of cores meeting certain threshold lengths, and the cancer detection rate per case. Iczkowski et al analyzed the relationship between prostate core length and cancer detection rate and found this relationship to be most significant in cores taken from the prostate apex. Biopsy location impacts core length as mid-gland and base cores were longer than apical cores.[12] Öbek et al performed a similar retrospective evaluation in the context of a 12-18 core scheme at a single center.[14] Core fragments were excluded from analysis as well as patients diagnosed with ASAP. Similar to our results, this research demonstrated that core length was 0.1 cm longer in patients diagnosed with cancer (1.2 vs 1.1 cm). Finally, Fiset et al conducted a retrospective review of 2 major hospital centers in Montreal which included biopsies from multiple urologists. Patient data were excluded for a previous diagnosis of cancer as well as fragmented cores. It was shown that cores harboring cancer were also approximately 0.1 cm longer than benign cores (1.4 vs 1.3 cm).[13] Whereas the diagnosis of cancer is of the utmost importance for the patient, the number of containers and/or cores with cancer is also important information to provide optimal care as multifocal or bilateral cancer may warrant more aggressive treatment. However, although the difference in length between cores with and without cancer is statistically significant, the difference is so small that it is not clinically usable and thus at this time there is no definitive total length of tissue nor individual core length that can be regarded as ideal.

Submission strategy for prostate biopsies differs between urologists, and no standard protocol for the number of prostate cores per container has been established. Our investigation showed that the number of containers utilized per case varied significantly between urologists, with no significant relationship to cancer detection rate. Importantly, for the single urologist who changed his submission protocol for no other reason than to reduce patient cost, a small, nonsignificant increase in cancer detection was noted when comparing 12-14 containers vs 6-9 containers. However, the amount of tissue measured by the anatomic pathology technicians in the early group (12-14 containers) was greater. As core biopsy strategy did not change, the difference may be due to the ease of measuring a single core from a single container rather than multiple cores within 1 container that can stick together, twist, and fragment. In 2004, Gupta et al compared biopsy specimens submitted in 1-2 containers to biopsy specimens in which each had a single core per container in a retrospective analysis of men who underwent a predominantly sextant prostate needle biopsy. With the use of a single core per container, the frequency of adenocarcinoma and HGPIN remained essentially the same, although the monthly rates of equivocal diagnoses (ASAP and ASAP/HGPIN) were significantly reduced.[16]

There are distinct advantages and disadvantages to submitting 1 core per container that have been described in past literature. Per Reis et al, although the number of cores removed was 21.5 per procedure, the mean counted by the pathologist was 24.1.[8] Therefore, fragmentation could lead to an increased count of cores with cancer and difficulty determining a definitive Gleason grade whereas submission of a single core per container may reduce the frequency of equivocal diagnoses.[8,9,16,17] Treatment decisions require correct core counts and tumor grading, and many have made the recommendation that no more than 1 core should be placed in a container to facilitate diagnostic accuracy.[3,8,9] Beyond the implications for cancer detection and tumoral characterization, increasing container number incurs more healthcare costs. According to a 2013 report by the Government Accountability Office, self-referring urology providers submitted more containers per prostate biopsy procedure compared to nonself-referring urology providers (12.5 vs 8.5 containers), and practices with higher numbers of containers had a lower cancer detection rate.[10,18] Reacting to the increased usage, in 2014 Medicare created a new code (G0416) for "saturation biopsies" in which 10-20 containers were provided, with a set revenue equating to a markedly decreased revenue per container. In 2015, Medicare designated this code for *all* prostate biopsies with reimbursement of approximately $600, similar to submitting 9 containers, regardless of core or container number. The 2016 Medicare fee schedule had further cuts to $500, equivalent to 7 containers. Thus, the submission of more than 7 containers will result in no further revenue but increased costs. The optimal biopsy strategy, which balances quality metrics and healthcare costs, has yet to be determined.[19]

There are several limitations to this retrospective study. Differences existed in surgeon practice preferences including the number of cores and containers submitted per case as well as the type of probe utilized. Statistical analyses were also performed controlling for surgeon, with no change in significant findings (data not shown). Resident involvement varied with surgeon, as described. Although this variability existed, the data in Table 2 support the notion that the variables analyzed were dictated by surgeon preference rather than resident participation. Another aspect to consider is the inclusion of fibromuscular tissue without prostate glands and anorectal tissue in the core length measurements. This is a limitation found in all studies thus far. Beyond these limitations, our analysis focused on the variation that exists in biopsy protocol and the impact of these variables on cancer detection rate. Our study did not explore the role of clinical variables such as prostate-specific antigen values, ethnicity, and physical examination findings. In

regard to our optimal number of containers submitted, our results suggest that reducing the number of containers did not affect the overall cancer detection rate. Our study was not powered to detect the degree of change, and future studies will be needed to further elucidate the relationship between the numbers of containers used and cancer detection. This study was limited in that we did not analyze the number of cores with cancer, the number of sites sampled, the laterality of the cancer detected, and the number of cores with each Gleason grade, all of which determine if a patient is a candidate for active surveillance.

CONCLUSION

This investigation demonstrated that the submitting urologist significantly impacts prostate biopsy variables including number of biopsy containers submitted, total core length, longest core length, and individual core length threshold values. We identified a significant relationship between the total amount of tissue per container and a diagnosis of cancer in that container. We also determined that when no other element of biopsy strategy was altered, reducing the number of containers was associated with a small, nonstatistically significant increase in cancer detection.

References

1. Presti JC Jr. Prostate biopsy: how many cores are enough? *Urol Oncol*. 2003;21:135-140.
2. Firoozi F, Nazeer T, Fisher HA, et al. Tissue-marking scheme for a cost-effective extended prostate biopsy protocol. *Urol Oncol*. 2009;27:21-25.
3. Bjurlin MA, Carter HB, Schellhammer P, et al. Optimization of initial prostate biopsy in clinical practice: sampling, labeling and specimen processing. *J Urol*. 2013;189:2039-2046.
4. Chun FK, Epstein JI, Ficarra V, et al. Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature. *Eur Urol*. 2010;58:851-864.
5. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Prostate Cancer Early Detection*. Version 1.2012. 2012. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed January 7, 2015.
6. Bertaccini A, Fandella A, Prayer-Galetti T, et al. Systematic development of clinical practice guidelines for prostate biopsies: a 3-year Italian project. *Anticancer Res*. 2007;27:659-666.
7. El-Hakim A, Moussa S. CUA guidelines on prostate biopsy methodology. *Can Urol Assoc J*. 2010;4:89-94.
8. Reis LO, Reinato JA, Silva DC, et al. The impact of core biopsy fragmentation in prostate cancer. *Int Urol Nephrol*. 2010;42:965-969.
9. Fajardo DA, Epstein JI. Fragmentation of prostatic needle biopsy cores containing adenocarcinoma: the role of specimen submission. *BJU Int*. 2010;105:172-175.
10. Mitchell JM. Urologists' self-referral for pathology of biopsy specimens linked to increased use and lower prostate cancer detection. *Health Aff (Millwood)*. 2012;31:741-749.
11. Van der Kwast TH, Lopes C, Santonja C, et al. Guidelines for processing and reporting of prostatic needle biopsies. *J Clin Pathol*. 2003;56:336-340.
12. Iczkowski KA, Casella G, Seppala RJ, et al. Needle core length in sextant biopsy influences prostate cancer detection rate. *Urology*. 2002;59:698-703.
13. Fiset PO, Aprikian A, Brimo F. Length of prostate biopsy cores: does it impact cancer detection? *Can J Urol*. 2013;20:6848-6853.
14. Öbek C, Doğanca T, Erdal S, et al. Core length in prostate biopsy: size matters. *J Urol*. 2012;187:2051-2055.
15. Bostwick DG, Qian J, Drewnowska K, et al. Prostate needle biopsy quality in reduction by dutasteride of prostate cancer events study: worldwide comparison of improvement with investigator training and centralized laboratory processing. *Urology*. 2010;75:1406-1410.
16. Gupta C, Ren JZ, Wojno KJ. Individual submission and embedding of prostate biopsies decreases rates of equivocal pathology reports. *Urology*. 2004;63:83-86.
17. Freedland SJ, Terris MK, Csathy GS, et al. Preoperative model for predicting prostate specific antigen recurrence after radical prostatectomy using percent of biopsy tissue with cancer, biopsy Gleason grade and serum prostate specific antigen. *J Urol*. 2004;171:2215-2220.
18. United States Government Accountability Office. *Action Needed to Address Higher Use of Anatomic Pathology Services by Providers Who Self-Refer*. GAO Publication No. 13-445. Washington, DC: U.S. Government Printing Office; 2013.
19. Centers for Medicare and Medicaid Services. *Physician Fee Schedule*. 2015. Available at: http://www.cms.gov/apps/physician-fee-schedule/license-agreement.aspx. Retrieved July 12, 2015.