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NEEDLE CORE LENGTH IN SEXTANT BIOPSY INFLUENCES PROSTATE CANCER DETECTION RATE

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ABSTRACT

Objectives. Prostate cancer detection in biopsies increases with the number of sites and total tissue sampled. Its dependence on needle core fragment length is uncertain.

Methods. We surveyed two consecutive series of sextant needle biopsies from two practices in 1998 to 2000: 251 patients from Pennsylvania (group P) and 1596 from Virginia (group V). We tabulated the gross needle core lengths per sextant site and classified the diagnoses as benign or into four nonbenign categories: high-grade prostatic intraepithelial neoplasia; atypical small acinar proliferation, suspicious; atypical small acinar proliferation, suspicious plus high-grade prostatic intraepithelial neoplasia; and cancer. Logistic regression analysis was used to correlate cancer or a nonbenign diagnosis with the total length (sum of six sites) and, after excluding the sites with more than one core, with the length per single core, and the anatomic site of origin (apex, mid-gland, base).

Results. The mean total tissue length sampled was 108 ± 27 mm (range 30 to 275) in group P and 81 ± 22 mm (range 30 to 228) in group V. Sextant sites with a single core contained a mean of 12.8 ± 3.5 mm tissue, with a 3.6-fold variation among the middle 95%. Group V core lengths at the apex averaged 11.8 mm, shorter ($P = 0.0001$) than mid (13.3 mm) or base (12.7 mm). A predictive value of longer length for a nonbenign diagnosis was noted in four of six sextants ($P < 0.04$), with trend strongest at the apex, for which detection was influenced by abnormal digital rectal examination ($P = 0.02$) or ultrasound ($P = 0.04$) findings.

Conclusions. The length of single cores sampled by sextant biopsy can vary more than 3.6-fold and represents a quality assurance consideration. The effect of length on cancer or nonbenign detection was maximal at the prostatic apex where the cores were shortest. UROLOGY **59:** 698–703, 2002. © 2002, Elsevier Science Inc.

Prostate cancer detection is optimized by sampling more anatomic sites. Various strategies have been successively devised for patterned sampling: bilateral biopsies, sextant sites, 8 to 15 biopsies,[1–4] and more.[5] Gross descriptions in a pathology report will disclose variations in core length, but the extent of variation and its influence on diagnostic yield, apart from its contribution to the total amount of tissue examined by the pathologist, remain to be quantified. Also, the yield of diagnostic abnormalities according to the anatomic site of the prostate (apex, mid, base) remains uncertain. In this study, we disclose: (a) the degree of core length variance in sextant biopsies; (b) the influence of this length variance on detection rate of abnormalities, namely cancer, atypical small acinar proliferation suspicious for malignancy (ASAP),[6–8] and high-grade prostatic intraepithelial neoplasia (HGPIN), on both a total tissue basis and sextant site single-core basis; and (c) the mean core length and detection rate of abnormalities according to anatomic site.

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MATERIAL AND METHODS

We retrospectively surveyed two sets of consecutive sextant, 18-gauge needle biopsies. We excluded any cases in which other than six (sextant) sites were sampled. Other exclusion criteria were prior prostate biopsy, presence of symp-

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toms, clinical stage other than T1c or T2, or prior antiandrogen or radiation therapy. From a 4-man Pennsylvania urology practice (group P), 251 cases were obtained from August 1, 1998 to May 31, 2000. Another series of 1596 cases originated from Bostwick Laboratories in Virginia (group V), a urologic pathology practice receiving specimens from more than 40 urologists, from November 9, 1999 to December 30, 2000. For each case, we tabulated the grossly measured core length (in millimeters) (recording up to three separate fragments per sextant site) according to both the single sextant site and in aggregate, and the single sextant and overall diagnoses. For group P only, the digital rectal examination result, abnormal ultrasound findings, and measured prostate volume were available in all but 1 case.

We placed the diagnosis of each biopsy into one of five categories: benign, ASAP, HGPIN, ASAP + HGPIN, and cancer. Diagnoses were grouped for statistical analysis as: (a) cancer versus noncancer and (b) benign versus nonbenign (includes ASAP and HGPIN, which carry 35% to 45% predictive values for cancer on repeat biopsy.[9,10]). Analysis then proceeded according to two approaches: (a) *Total tissue analysis.* We used Statistical Analysis System software (SAS Institute, Cary, NC) to analyze core length by site (apex, mid, base) using the general linear model. Analyses involving group V diagnoses were made to fit a cumulative logit mixed model (NLMIXED procedure). This allowed us to model diagnoses as functions of the covariates and include a random effect for each subject. This approach removed the random variability within each patient, arising from there being six length observations per patient. Core length was treated as a continuous variable, according to these covariates: aggregate length of all six sites and of each sextant site, ln (age), ln (PSA), and six anatomic locations (left/right apex, mid-prostate, base). (b) *Single core analysis.* Some of the anatomic sites in our data spreadsheet had more than one core fragment, possibly reflecting sampling by more than one pass of a needle. Lengths and diagnoses from these sites were deleted and excluded from analysis with the exception that if a second core was 3 mm or less, it was presumed to arise from fragmentation and was added to the length of the longer core. This generated gaps in the data, precluding per-patient analysis, and necessitated running standard logistic regression on individual sites. Core fragment length was reanalyzed with the covariates above.

Finally, the gun needle length was known for group P cases (3 urologists used a 20-mm gun needle and one used a 25-mm needle) but not for group V. We correlated the group P apparatus length with the diagnosis by the unpaired two-tailed *t* test. The *t* test was also used to compare the mean core length and diagnostic frequencies from the three anatomic sites in both groups. The logistic procedure was used to assess the interactions of prostate volume, abnormal digital rectal examination findings, and abnormal ultrasound findings with the needle lengths for the group P diagnoses.

RESULTS

Tissue Length Variation

Mean total tissue length sampled per case was 108 ± 27 mm (range 30 to 275) in group P versus 81 ± 22 mm (range 30 to 228) in group V (Table I). This reflected sampling of more than one core in 30% of group P sites but in only 5% of group V sites. Two cases in group P (1%) had total tissue of less than 50 mm long; 65 (4%) did so in group V. After excluding all data from the sites with multiple cores, the tissue per sextant site averaged 12.8 ± 3.5 mm. Figure 1 shows the distribution of single cores. After excluding extreme observations, the middle 95% of cores ranged from 5 to 18 mm. For both groups, we calculated the tissue length according to anatomic site of the biopsies. A comparison of sites with a single core (Table I) revealed shorter average lengths for the apex than mid-gland and base ($P = 0.02$, group P and $P = 0.0001$, group V). Even more striking, when the lengths of tissue (group V) were grouped into 2 to 10 mm, 11 to 20 mm, and greater than 21 mm, the percentage of 2 to 10-mm cores was greatest at the apex, 35% ($P = 0.0001$) compared with 17% for the mid-gland and 24% for the base.

Influence of Tissue Length on Diagnosis

Overall benign and nonbenign diagnoses for groups P and V are listed in Table I. The only diagnosis whose frequency depended on anatomic site was HGPIN, which was less frequent in group P at the apex (1.8%) than at the mid-gland (3.5%) or base (6.2%) ($P < 0.01$, *t* test). A similar trend existed in group V ($P = 0.30$).

Total tissue analysis involved three approaches. The first compressed the diagnoses into cancer versus noncancer groups. Analysis was first done according to the total tissue length per patient, yielding nonsignificantly increased cancer detection with length ($P = 0.380$ in group P, $P = 0.148$ in group V). Group V data were also analyzed according to anatomic site, showing increased cancer detection with longer tissue length ($P = 0.15$), but this was significant only at the apex ($P = 0.0009$). On a total tissue basis, the increase in cancer diagnosis with longer length was, by logistic regression analysis:

$$\frac{\Pr(\text{no cancer in tissue length } x)}{\Pr(\text{cancer in tissue length } x)} = e^{6.92}\left[\frac{\Pr(\text{no cancer in tissue length } x + 1\text{ cm})}{\Pr(\text{cancer in tissue length } x + 1\text{ cm})}\right]$$

where Pr equals probability and e equals 2.718. . . . ln (patient age) interacted with the total length to increase cancer detection ($P = 0.30$ in group P, $P = 0.16$ in group V). This effect was maximal at ln (age) + 1 standard deviation, or age 74.6 for group V. Cancer diagnosis correlated with abnormal digital rectal examination findings ($P = 0.0004$) and smaller prostate volume ($P < 0.0001$); these covariates were available only for group P. The second outcome analysis (group V only) compared benign versus HGPIN ± ASAP versus cancer. The total length correlated with the diagnosis ($P = 0.19$), again significantly at the apex ($P = 0.0011$). The third outcome analysis (group V only), comparing benign versus ASAP ± HGPIN versus cancer, showed significantly more detection of cancer/ASAP with a longer total tissue length ($P = 0.038$).

TABLE I. *Mean length and diagnosis of prostate needle cores by anatomic site*

Anatomic Site	Apex	Mid	Base	All Sites	Total Tissue (Sum of All Sites and Fragments)
Group P*					
Mean length of all fragments (mm)	15 ± 6	22 ± 9	17 ± 7	18.1 ± 8.0	108 ± 27
Cancer (% of diagnoses)	13.5	16.5	14.9	—	44
Samplings of site by single core (%)	82.3	47.0	79.7	69.7	—
Mean single core length (mm)	13.5 ± 3.7†	14.6 ± 3.3	14.5 ± 3.1	14.2 ± 3.4	—
Diagnoses based on single cores (%)					
Benign	82	82	78	42	—
HGPIN	2‡	3‡	6‡	8	—
ASAP	1	0	1	3	—
ASAP+HGPIN	0	0	0	3	—
Cancer	15	17	15	44	—
Group V§					
Mean length of all fragments (mm)	12 ± 4	16 ± 8	13 ± 3	13.6 ± 3.7	81 ± 22
Cancer (% of diagnoses)	13.8	15.4	14.8	—	35
Samplings of site by single core (%)	99.5	84.4	99.5	94.5	—
Mean single core length (mm)	11.8 ± 3.4¶	13.3 ± 3.3	12.7 ± 3.2	12.6 ± 3.3	—
% cores 2–10 mm	35**	17	24	25	
% cores 11–20 mm	64	67	76	69	
% cores >21 mm	0.6	16**	0.4	8	
Diagnoses based on single cores (%)					
Benign	78	74	75	47	—
HGPIN	6	7	8	13	—
ASAP	2	2	1	3	—
ASAP+HGPIN	0.2	0	0.1	2	—
Cancer	14	16	15	35	—

KEY: HGPIN = high-grade prostatic intraepithelial neoplasia; ASAP = atypical small acinar proliferation suspicious for cancer.
* *251 patients, mean age 65.0 ± 7.9 yr, range 45–90.*
† P *<0.02, pairwise comparisons with mid-gland and base, general linear model (SAS system).*
‡ P *<0.01,* t *test, HGPIN significantly less frequent at apex and more frequent at base.*
§ *1596 patients, mean age 65.7 ± 8.6 yr, range 42–93.*
¶ P *<0.0001, pairwise comparisons with mid-gland and base, general linear model (SAS system).*
** P *<0.0001,* t *test.*

Single-core analysis revealed that a mean 12.8 ± 3.5 mm of tissue was sampled among all sites (mode 15 mm), with a 3.6-fold variation within the middle 95%. Figure 2 demonstrates the positive correlations of different magnitudes between core length and detection of cancer/nonbenign findings. Table II shows that the positive correlation between the length and detection was significant ($P \leq 0.05$) in both apices and bases. Abnormal digital rectal examination or ultrasound findings interacted significantly with length in the apices but not at other anatomic sites (Table II). Prostate volume, when included in the analysis, demonstrated no significant influence on core length-diagnosis relationships.

Effect of Needle Length

The 25-mm needle was used in 45 patients in group P (270 sextant biopsies). Compared with the 20-mm needle, it sampled more tissue per sextant (19.6 versus 17.8 cm; $P = 0.0007$), in longer fragments (13.1 versus 12.2 cm; $P < 0.0001$). The longer needle did not, however, detect more cancer/nonbenign findings (both, $P = 0.12$).

COMMENT

We have shown, in two independent sample populations, that sextant biopsies sample widely varying lengths of single cores and total tissue. As shown previously,[1–5] sampling more total tissue increases cancer detection, but we now reveal a dependence of nonbenign diagnoses on single-core length. These trends were highly significant for biopsies of the apices and bases. Some investigators consider 50 mm of aggregate core length as an "adequate" sample,[11] about 8.3 mm/core. We found an overall tissue sample of less than 50 mm in 2 group P cases (0.8%) and 65 group V cases (4%). Notably, 25% of single cores (groups P and V) had 10 mm or less of tissue. The relative adequacy of tissue lengths from a standard needle can be judged (Fig. 2). For example, a 20-mm core from the right apex provides a 0.27 probability of cancer detection ver-

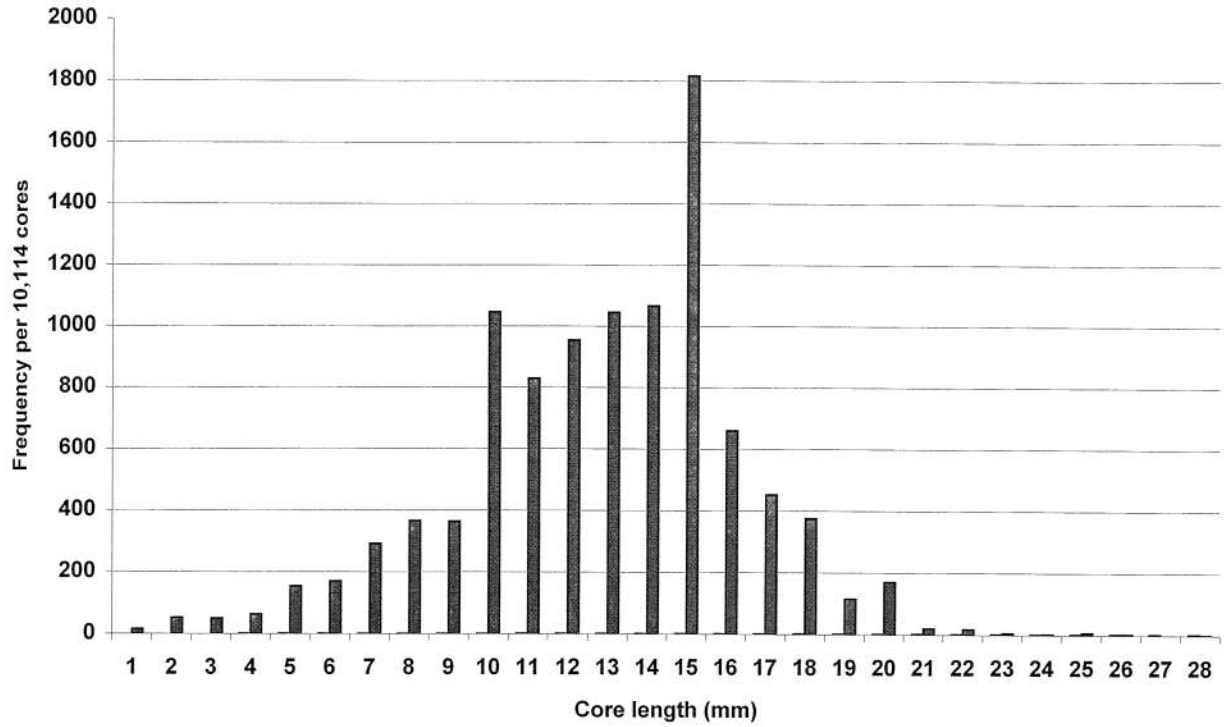

FIGURE 1. *Frequency of length distribution of single prostate biopsy needle cores (combined group P and group V). A mean 12.8 ± 3.5 mm was sampled.*

sus 0.18 for 10 mm. 0.5% of single-core sextant biopsies were greater than 20 mm; that amount of tissue usually represented multiple passes of the needle, data we excluded. Also, we did not tabulate which specimens were aglandular or devoid of prostatic tissue.

Protocols proposed to increase the diagnostic yield in recent years have focused on the number of sites sampled. The diagnostic yield of sextant prostatic biopsies is as much as 43% higher than the yield with two or fewer biopsies.[12–14] Biopsy of 12 sites yielded 29% more cancers than the sextant approach, all of which were greater than 0.5 mL in volume.[1] "Saturation" protocols (14 to 45 sites) after previous negative sextant biopsy detect cancer in 34% of patients.[5] The diagnostic yield of biopsy has also been optimized by ultrasound "targeted" biopsies[2] and the addition of four far-lateral peripheral zone biopsies[3] or of posterolateral biopsies.[4] By restricting our scope in the present study to all-sextant biopsies, we demonstrated that sampling variance depends at least as much on core length as it does on sampling protocols, which we have shown remain heterogeneous among urologists.[15] This severalfold variance in single-core length may explain some discrepant findings in studies using modern, more than 6-site, protocols.[1–5]

An inherent limitation of our study was our inability to know how many cores per site the urologist sampled; the patient charts lacked these data. Needle cores often fragment on arrival in the pathology laboratory. (For this reason, we report the percentage of cancer per specimen rather than per core in our diagnostic reports.) Single-core analysis overcame this by excluding data that may have resulted from more than 1 needle pass per site. This showed a dependence of the detection rate of cancer/nonbenign findings solely on length of needle penetration, with the highest significance at the apex. Another unmeasured source of variance in the cancer yield is the processing of the needle biopsy by the histotechnologist. This may reduce the length of tissue appearing on microscopic slides, although we obtained multiple step-levels at different planes, as recommended,[14] to minimize this problem.

The dependence of diagnosis on tissue length was strongest at the prostatic apices and was influenced by abnormal digital rectal examination or ultrasound findings at the apices only (constrained by availability only in group P). Anecdotally, the apex may be the hardest site to biopsy because of spatial constraints as one approaches the urogenital diaphragm. Not only were apical cores shorter than the mid-gland or base cores in our study, but the apex was the only site in which tissue length correlated strongly with cancer or nonbenign detection. The apex appeared particularly prone to inadequate sampling, with twice as many cores less

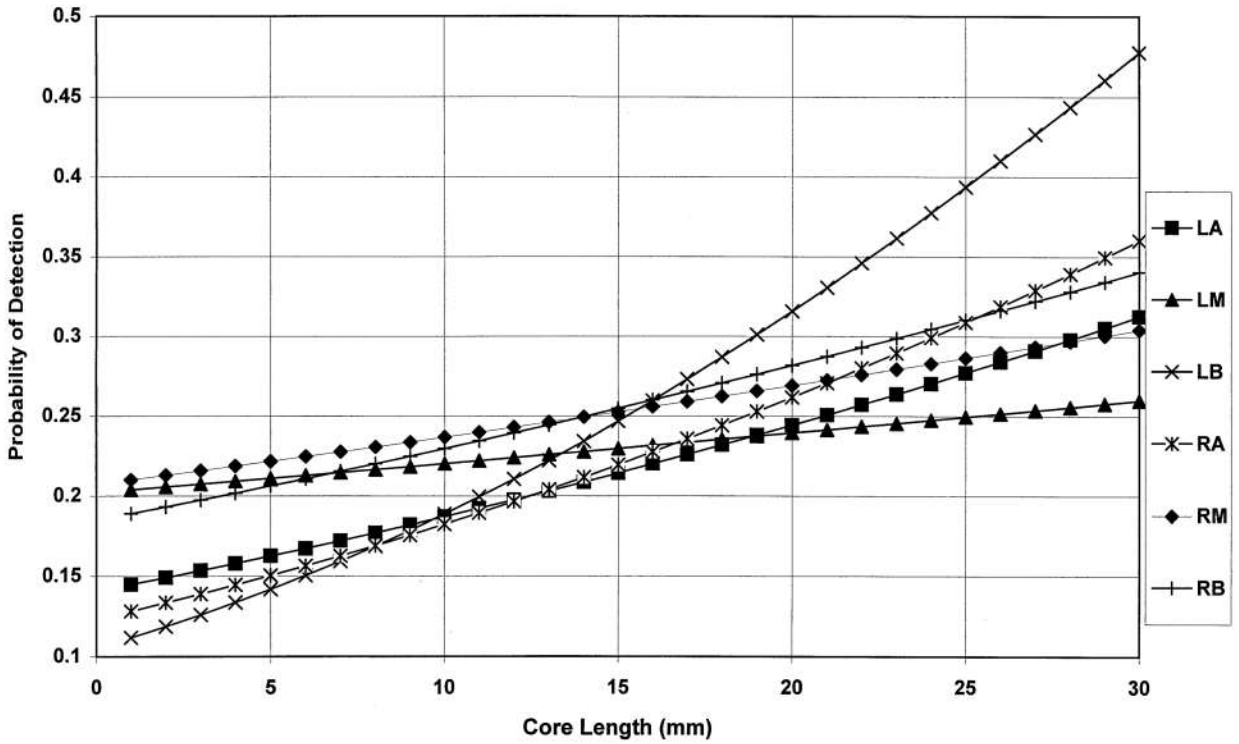

FIGURE 2. *Six curves show the increase in detection rate of nonbenign findings at each sextant site over the range of core length (1 to 28 mm) in the study (combined group P and group V). LA = left apex, LM = left mid-prostate, LB = left base, RA = right apex, RM = right mid-prostate, RB = right base.*

TABLE II. ***Significance (P values) of the positive predictive value of single core length for cancer or nonbenign diagnosis (both groups)***

	Apex		Mid-Prostate		Base	
Diagnosis	**Left**	**Right**	**Left**	**Right**	**Left**	**Right**
Cancer	0.05*	0.002*	0.06	0.22	0.006*	0.042*
Nonbenign	0.02*	0.004*	0.16	0.11	0.0003*	0.043*
Influence of abnormal digital rectal examination on predictive value for cancer†	0.007*	0.016*	0.23	0.26	0.14	0.13
Influence of abnormal ultrasound on predictive value for cancer†	0.010*	0.036*	0.06	0.33	0.06	0.29
Influence of prostate volume‡ on predictive value for cancer	0.1–0.5	0.1–0.4	0.1–0.9	0.3–1.0	0.06–0.5	0.3–0.7

Nonbenign includes atypical small acinar proliferation suspicious for but not diagnostic of malignancy and high-grade prostatic intraepithelial neoplasia.
* *Significant P value.*
† *Based on group P only.*
‡ *Ultrasonographically measured prostate volume (group P) was stratified for analysis as 0–29, 30–39, 40–49, 50–59, 60–69, and >70 cm^3.*

than 10 mm as for the mid-gland. The apex lacks a capsular boundary and has interdigitating urogenital diaphragm skeletal muscle, so that apical biopsies may often consist solely or primarily of aglandular, fibromuscular tissue. Our study did not address this hypothesis. Because the apex accounts for 64% of margin positivity at prostatectomy,[16] apical biopsy adequacy demands special attention. Submitting each anatomic site in separate jars, as recommended,[15] facilitates this quality assurance measure. Prostate size is a well-known consideration in choosing the number of cores to sample.

Size did not interact significantly with needle core length to influence diagnosis in our study. This finding may reflect hyperplasia of the transition zone as the main cause of larger prostates, exerting little influence on needle sampling of the cancer-harboring 1 to 2 cm of the peripheral zone. A concomitant, unexpected finding was that less HGPIN was detected at the apex than at other sites. Prior studies indicated that HGPIN was located in the nontransition zones in 63% to 65% of cases and all zones in 36%.[17,18] Our finding suggests either a tendency to undersample HGPIN at the apex, possibly because of frequent aglandular samples, or that the apex may harbor HGPIN less often than the other sites.

Finally, the 25-mm needle sampled more tissue than the 20-mm needle, although nonbenign detection rates were statistically similar. This attribute was evaluated only in group P, however, and the small sample size of group P may have precluded detection of significant differences.

CONCLUSIONS

Significant trends were noted for more detection of cancer and nonbenign findings in sextant prostate biopsies as longer single cores were sampled, particularly at the apex. Biopsy tissue length is at least as influential as the number of sites sampled and should be examined before submission for quality assurance.

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