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Risk Factors and Predictors of Prostate Cancer in Men with Negative Repeat Saturation Biopsy

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ABSTRACT

INTRODUCTION: Despite evidence of increased cancer detection during repeat biopsy, no reports have addressed the likelihood of cancer detection after a negative repeat saturation biopsy or the risk factors that would warrant performing additional saturation biopsies. The investigators tested the hypothesis that a narrowly defined population with 2 biopsies showing no prostatic intraepithelial neoplasia (PIN) or atypia is effectively ruled out as having a risk of prostate cancer.

METHODS: The authors retrospectively evaluated 655 patients that had repeat saturation prostate biopsies from April 2002 to January 2009. *Repeat saturation biopsy* included patients who had 2 or more biopsies with at least the most recent being a saturation biopsy of 20 cores or more. Repeat biopsy was performed if prostate-specific antigen (PSA) rose significantly after the last biopsy. The variables analyzed were PSA, age, race, number of previous biopsies, number of cores taken, inflammation on pathology specimens, total prostate volume, and digital rectal exam (DRE) results.

RESULTS: Of the 655 patients with repeat saturation biopsies, 236 were *truly negative*, defined as no cancer, atypia, or PIN. In a mean follow-up of 33.2 months (range, 0-70) 70 of the 236 patients (30%) clinically required a repeat saturation biopsy. Of these, 10 (4.2%) developed prostate cancer. Most patients who were diagnosed with cancer had a PSA >10 ng/mL at the first saturation biopsy, as opposed to PSA <10 in the group that did not develop prostate cancer. In a multivariate analysis comparing patients that developed prostate cancer with those that remained cancer free, significant predictors of future prostate cancer were: higher number of previous biopsies (P = .006), higher number of cores taken (P = .02), decreased total prostate volume (P = .03), and change in PSA (P = .0002). PSA at first saturation biopsy (P = .006) and PSA at final follow-up evaluation (P = .0001) were significantly different between patients with and without prostate cancer.

CONCLUSION: Patients with a history of negative saturation biopsy have around a 4% chance of being diagnosed with prostate cancer over a mean follow-up period of 33 months. Biopsy detection of prostate cancer in those men who had an additional biopsy because of elevated PSA or change in DRE resulted in a detection rate of 14%, which is clinically substantial. Patients with a rising PSA may warrant a lower threshold for subsequent repeat saturation biopsy. Saturation biopsy as repeat biopsy detects almost all significant cancers and may obviate the need for future biopsy in men who are carefully followed with clinical examinations.

KEYWORDS: Prostate biopsy; Saturation biopsy; Prostate-specific antigen (PSA)

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original study

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INTRODUCTION

The diagnostic yield of prostate biopsies has been improved with the use of a systematic transrectal ultrasound-guided prostate biopsy technique [1]. Refinements to this technique include directing the biopsies more laterally to increase diagnostic yield and increasing the number of cores obtained from the original 6 to extended schemes involving 10-14 in most current series [2-4]. A reported 25% increase in the detection rate of prostate cancer has been associated with laterally directed extended biopsies [5-7].

Saturation biopsy (typically defined as biopsy schemes involving 20 or more cores) has been shown to be useful as a repeat biopsy technique. The prostate cancer detection rate is increased in repeat biopsy cases in which a saturation biopsy is used instead of a 6-12 core biopsy. The prostate cancer detection rate doubled in a small series of 91 patients with repeat saturation biopsies [8].

The application of local anesthesia is known to reduce the pain and discomfort associated with routine in-office biopsy [9,10]. The present and previous authors have shown that saturation biopsy can be performed safely and effectively in the office with a significant diagnostic yield, even in patients with previous extended biopsy schemes [5,11].

Despite evidence of its utility for increased cancer detection during repeat biopsy, no reports have addressed the likelihood of cancer detection after a negative repeat saturation biopsy. The purpose of the present investigation was to report the likelihood of cancer detection after a negative repeat saturation biopsy and the risk factors that would warrant performing additional saturation biopsies. The participants were patients who had 2 or more biopsies with at least the most recent being a saturation biopsy of 20 cores or more. The hypothesis was that this narrowly defined population with 2 biopsies showing no prostatic intraepithelial neoplasia (PIN) or atypia is effectively ruled out as having a risk of prostate cancer, so that there would be near certainty of a benign diagnosis.

METHODS

Participants

As part of an ongoing institutional review board approved prostate biopsy registry, 655 patients underwent repeat saturation prostate biopsies from April 2002 to January 2009. *Repeat saturation biopsy* included patients who had 2 or more biopsies with at least the most recent being a saturation biopsy of 20 cores or more. After the second biopsy (the first repeat biopsy) prostate-specific antigen (PSA) was repeated yearly; repeat biopsy was performed if PSA rose significantly after the last biopsy.

The authors excluded all patients who had a previous biopsy that was positive for prostate cancer, prostatic intraepithelial neoplasia (PIN), or atypia. Of the 655 patients with repeat saturation biopsies, 460 patients (70.2%) did not have evidence of cancer in their biopsies. The authors identified 236 patients with a *truly negative* (no atypia, PIN, or cancer in the specimen) repeat saturation biopsy. The mean number of previous biopsies was 2.65 (range, 2-6). The mean patient age was 64 years (range, 50-85 years). Patients self-identified their race as white (n = 215), African-American (n = 19), and other (n = 2).

Procedure

Informed consent was obtained. All patients were instructed to discontinue anticoagulants 5 days before biopsy, but they were allowed to continue any aspirin or nonsteroidal anti-inflammatory drugs. The patients had discontinued warfarin and clopidogrel prior to biopsy. No enemas were used. Each patient received a single dose of fluoroquinolone before biopsy.

Patients were placed in the left lateral decubitus position. The ultrasound probe was inserted transrectally. A 22-gauge 7-inch spinal needle (Becton Dickinson, Franklin Lakes, NJ, USA) was placed at the base of the prostate where the prostatic sensory nerves enter it, or at the prostate apex. Placement depended on surgeon preference, as previously described [12,13]. Ultrasound examination and volume calculations were then performed. A total of 20 or more biopsies were taken without delay using a spring-loaded biopsy gun. Biopsies were evenly distributed throughout the prostate and included any visible abnormalities. A board-certified pathologist interpreted all slides and the urological pathology team reviewed any equivocal results during regularly scheduled follow-up sessions.

Data Analysis

The outcome measures were PSA, age, race, number of previous biopsies, number of cores taken, inflammation on pathology specimens, total prostate volume, and digital rectal exam (DRE) results. Data were recorded in a Microsoft Access® database. The measures were compared between the group of patients that developed prostate cancer at some point in the future (cases group) and those that remained prostate cancer free during the follow-up interval (comparison group). Differences between outcomes were examined with either the Wilcoxon rank-sum test for continuous variables or Fisher's exact test for categorical variables. The association between variables and the outcome were expressed as odds ratios (OR) and their 95% confidence intervals (95% CI).

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Table 1. Prostate-Specific Antigen (PSA) and Prostate Volumes for Patients With Negative Repeat Saturation Biopsy (No PIN, Atypia, or Cancer) (N = 236).
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Variable	Mean	Range
PSA before biopsy (ng/mL)	7.7	0.2-31
PSA after biopsy (ng/mL)	6.9	0.32-43.9
Total prostate volume (cc)	53	11-206
Central prostate volume (cc)	26	15-37

Table 2. The Number of Subsequent Saturation Biopsies Taken After the Initial Truly Negative Repeat Saturation Biopsy (N = 236).
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Number of Subsequent Biopsies	n	Number Positive for Cancer	
		n	%n
None	0	0	0
One (3rd overall)	168	6	3
Two (4th overall)	48	4	6.7
Three (5th overall)	14	0	0
Four (6th overall)	6	0	0

RESULTS

All patients tolerated complete biopsies, and a mean of 21 cores (range, 20-32) was obtained. The patient characteristics for PSA and prostate volumes are shown in Table 1.

The mean follow-up was 33.2 months (range, 0-70 months). Table 2 shows the number of subsequent saturation biopsies taken after the initial truly negative repeat saturation biopsy. Of the original 236 patients, 70 patients (30%) clinically warranted a second saturation biopsy due to abnormal DRE or increasing PSA. The repeat biopsy was chosen on a case-by-case basis at the attending physician's discretion. The majority of the 236 patients (95.8%) remained prostate cancer free; 10 patients (4.2%) were diagnosed with prostate cancer at some point during the follow-up interval.

Table 3a contains the results of the univariate analyses for continuous variables; Table 3b contains the results for categorical variables. The analyses showed that 4 variables were significant predictors of subsequent diagnosis of prostate cancer: number of previous biopsies (P = .006), number of cores obtained (P = .02), total prostate volume(P = .03), and change in PSA (P = .0002). The significance of these variables was confirmed by multivariate analysis (Table 4). In the present analysis, 1 additional biopsy session increased the odds of finding subsequent prostate cancer by 2.8; 1 additional core per session increased the odds of finding subsequent prostate cancer by 1.4; one additional mL of prostate volume decreased the odds of finding subsequent prostate cancer by 0.1; and 1 additional

Table 3a. Median and Range of Continuous Variables for Patients With and Without Prostate Cancer; Probability of Significant Group Differences (N = 236).
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Variable	Total (N = 236)		Prostate Cancer				P
			Yes (n = 10)		No (n = 226)		
	Median	Range	Median	Range	Median	Range	
Age (years)	63	59-70	67	63-69	63	59-70	.4
Previous biopsy (number)	1	1-2	2	2-3	1	1-2	.006
Cores (number)	20	20-22	23	20-25	20	20-22	.02
Total prostate volume (cc)	47	31-70	25	20-40	47	32-71	.03
PSA at first biopsy[a] (ng/mL)	6.2	4.3-9.3	13.7	9.2-15.2	6.0	4.3-9.0	.006
PSA at final biopsy[a] (ng/mL)	5.3	3.7-8.0	19.3	9.6-34.5	5.2	3.6-8.0	.0001
Change in PSA[b] (ng/mL)	-0.5	-2.6-1.0	5.0	2.5-11.0	-0.6	-2.9-0.7	.0002

Abbreviation: PSA, prostate-specific antigen.
[a]There was a difference between PSA at first saturation biopsy and PSA at final biopsy in patients with cancer (P = .0002), without cancer (P = .0001), and overall (P = .002).
[b]PSA increased in patients with cancer (P = .002).

Table 3b. Number of Patients With and Without Prostate Cancer for Categorical Variables; Probability of Significant Group Differences (N = 236).
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Variable	Total (N = 236)		Prostate Cancer				*P*
			Yes (n = 10)		No (n = 226)		
	n	%N	n	%n	n	%n	
Race							.8
African-American	19	8	2	13	17	8	
White	215	91	13	87	202	91	
Other	2	1	0	0	2	1	
Inflammation on specimen	112	52	4	50	108	52	.9
Abnormal digital rectal exam	17	8	0	0	17	8	.4
Hypoechoic lesions	7	3	0	0	7	3	.6

ng/mL of PSA increased the odds of finding subsequent prostate cancer by 1.3. The average prostate volume was 25 cc (range, 20-40 cc) at the time of prostate cancer detection. The variables of age, race, inflammation on pathology specimens, abnormal DRE, and number of hypoechoic lesions were not significant predictors of subsequent prostate cancer diagnosis.

The PSA at the first and final saturation biopsies for the patients with and without prostate cancer is also contained in Table 4. PSA at first saturation biopsy (*P* = .006) and PSA at final follow-up evaluation (*P* = .0001) were significantly different between groups. The average change in PSA for those patients developing prostate cancer was 5 ng/mL (2.5 ng/mL-11 ng/mL) over the follow-up period. Most patients who were diagnosed with cancer had a PSA >10 ng/mL at the first saturation biopsy, as opposed to PSA <10 ng/mL in the group that did not develop prostate cancer (see Table 1). Similarly, the PSA at final follow-up was markedly different between the groups (mean of 19.3 and 5.2 ng/mL for the patients developing cancer and not developing cancer, respectively). Finally, the Gleason scores (GS) for the patients with cancer were: GS-6 (n = 6), GS-7 (3+4) (n = 2), and GS-8 (4+4) (n = 2).

DISCUSSION

It has been shown that the incidence of cancer is comparably detected for the initial biopsy, whether using a saturation technique or a 10-core technique (44.6% vs 51.7%, respectively) [14]. Additionally, a saturation technique does not appear to decrease the likelihood that cancer will be detected during subsequent biopsy [15]. In contrast, on repeat biopsy, a saturation technique appears to offer significant benefit and has been shown to increase the ability to detect prostate cancer [5,16-18].

Once a repeat saturation biopsy is found to be benign, the question of which patients to rebiopsy and when to perform the rebiopsy still remains undefined. The results of the present study suggest that patients with a history of negative repeat (ie, at least the second overall) saturation biopsy of $\geq$ 20 cores have a < 4% chance of receiving a later diagnosis of prostate cancer. The authors did a rebiopsy on 70 patients in this group because of clinical suspicion of prostate cancer (increasing PSA

Table 4. Multivariate Analysis: Odds Ratio of Developing Prostate Cancer after Repeat Saturation Biopsy; Probability of Significant Comparison (N = 236).
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Variable	Odds Ratio	95% CI	*P*
Previous biopsy (number per biopsy)	2.8	1.1-6.8	.02
Cores (number per core)	1.4	1.1-2.0	.03
Total prostate volume (per mL)	0.9	0.8-1.0	.007
Change in PSA (per ng/mL)	1.3	1.1-1.4	.0006

Abbreviations: PSA, prostate-specific antigen; CI, confidence interval.

or change in DRE); 10 patients (14%) were diagnosed with prostate cancer. This detection rate is clinically substantial. The authors then sought to determine which characteristics were associated with a significant likelihood of developing prostate cancer after a negative saturation biopsy in order to further decrease the need for unnecessary repeated biopsies. A higher number of previous biopsies, greater number of cores, and an increase in PSA levels of 2.5 ng/mL are all associated with the future development of prostate cancer in patients with negative repeat saturation biopsy over an average of 33 months of follow-up (range, 0-70 months).

Although a greater number of cores would logically be associated with a higher likelihood of finding prostate cancer during such procedures, the finding that multiple prior biopsy sessions suggest a higher risk of cancer is counterintuitive. The authors believe that this is explained by the fact that the patients are likely to require significant clinical suspicion before a decision is made to biopsy following multiple negative biopsies.

It should be noted that the only cases of cancer found in the present study were patients undergoing biopsy for a PSA change of 2.5-11 ng/mL. Of the 209 patients with PSA elevation of 0.7 or less, no cancer cases were identified (including all 43 patients in the group that underwent repeat biopsy). The authors found that larger prostate volumes suggested lower odds of finding prostate cancer on subsequent biopsy. This may be due to a sampling density phenomenon similar to that used to explain the excess of high-grade cancers among the finasteride-assigned participants in the Prostate Cancer Prevention Trial [19]. Alternatively, if it is assumed that men with large prostates and those with small prostates have equal rates of prostate cancer and that men with large prostates are more likely to be biopsied because of elevated PSA due to benign prostatic hyperplasia (BPH), the cancer detection rate would be artificially lower in the group with large prostates simply due to a larger denominator of biopsied prostates.

The present data suggest that 30% of patients with a *truly negative* (no atypia, PIN, or cancer in the specimen) repeat saturation biopsy will have further clinical suspicion of prostate cancer requiring further biopsy. Additionally, approximately 4% of this original population with truly negative saturation biopsy will have undiagnosed prostate cancer. Although these cancers are likely to be low-volume and low-risk, those patients with significantly increasing PSA, increased number of previous biopsies, and decreased prostate volume of $\leq$ 25 grams should be followed more closely. It seems reasonable to consider a subsequent biopsy even in this highly selected group with a negative repeat saturation biopsy. However, in those patients without clinical predictors, a negative saturation biopsy decreases the likelihood of future development of prostate cancer. Observation appears justified unless significant clinical changes suggest the likelihood of a new prostate cancer diagnosis. In addition, given that the majority of patients with 1 negative repeat saturation biopsy remain cancer free, it can be concluded that in the vast majority of men followed with the PSA and DRE protocol described, a benign diagnosis can be made with 1 repeat saturation biopsy alone. This precludes the expense and risks associated with multiple repeat biopsy procedures.

The present study is limited by its reliance on a prostate biopsy registry population that may not be reflective of the overall population. Many patients were treated through referral to a tertiary care center based on high suspicion of malignancy following prior negative biopsy. However, all saturation biopsies were performed at the authors' institution by one of 2 experienced urologists, so reliability of the sampling technique appears to be high. Physicians who do not use the regimen of PSA and DRE described in this investigation may find different results. Another limitation is that 4 independent variables were incorporated into a multivariate analysis in which the endpoint was reached in only 10 patients. However, the total number of patients needed in order to significantly raise the number of patients who eventually developed prostate cancer would be too large to obtain at a single institution with a low number of operators and similar sampling techniques. Finally, the authors of the present study compared patients that were and were not subsequently diagnosed with prostate cancer; however, only 30% of the patients had a repeat biopsy and the range of follow-up was 0-70 months. It is possible that there is a percentage of men that did not get rebiopsied and harbor prostate cancer. However, given that only 10 patients ultimately developed prostate cancer after a negative repeat saturation biopsy, it seems unlikely that a negative repeat saturation biopsy in a population of patients not clinically suspicious of prostate cancer would be reversed.

Conclusion

Saturation biopsy as a repeat biopsy strategy detects almost all significant cancers and may obviate the need for future biopsy in men who are carefully followed with clinical examinations. Furthermore, a saturation biopsy is justified in men who warrant a repeat biopsy after their initial biopsy. An additional follow-up saturation biopsy should be performed in men with a high suspicion for malignancy. Subsequent biopsy appears justified in men whose PSA rises 2.5 ng/mL or greater. This recommendation is based on the finding that all 10 patients

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diagnosed with cancer in this study had PSA changes in that range and PSA values of 10.0 ng/dL or higher. It should be noted that most patients who were diagnosed with cancer had a PSA >10 ng/mL at the first saturation biopsy, as opposed to PSA <10 in the group that did not develop prostate cancer. Similarly, the PSA at final follow-up was markedly different between the groups. The authors conclude that a single office-based saturation biopsy as a repeat biopsy strategy may obviate the need for serial repeat biopsies. Repeat biopsies may be reserved for patients suspected of having a high risk of undiagnosed prostate cancer, such as those with a rapidly rising PSA. Furthermore, patients with a negative saturation biopsy (no prostate cancer, PIN, or atypia) have a consistent likelihood of having a prostate cancer diagnosis (14%), particularly if the PSA is above 10 ng/mL and continues to increase. Conversely, for all other patients followed with the protocol described, the risk of detecting cancer appears to be low.

Conflict of Interest: none declared

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