The Association of Previous Prostate Biopsy-Related Complications and the Type of Complication with Patient Compliance with Re-Biopsy Scheme

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Abstract:

Introduction: Prostate biopsy complications have important consequences that may affect patient compliance with re-biopsy schemes; however, this has not been studied in earnest. Thus, we evaluated whether previous prostate biopsy-related complications and the type of complication were associated with repeat prostate biopsy compliance in a clinical trial with study-mandated systematic biopsies.

Materials and Methods: Retrospective analysis of 4,939 men ages 50-75 who underwent a 2-year prostate biopsy and were recommended to undergo the 4-year prostate re-biopsy in the Reduction by Dutasteride of prostate cancer Events (REDUCE) study. The analyzed biopsy complications were: hematuria, urinary tract infection (UTI), acute urinary retention (AUR) and hematospermia.

Results: A total of 260 (5.3%) men had a 2-year prostate biopsy-related complication, including 180 (3.6%) hematuria, 36 (0.7%) UTI, 26 (0.5%) AUR, and 102 (2.1%) hematospermia. A total of 474 (9.6%) men were noncompliant with the 4-year re-biopsy. In univariable analysis, any previous complication (OR=1.56, 95%CI=1.08-2.24, P=0.018), UTI (OR=2.72, 95%CI=1.23-6.00, P=0.013), AUR (OR=4.24, 95%CI=1.83-9.81, P=0.016) and hematospermia (OR=1.78, CI=1.03-3.06, P=0.037) were associated with re-biopsy noncompliance. Hematuria was not associated with re-biopsy noncompliance (OR=1.19, CI=0.74-1.91, P=0.483). Results were unchanged in multivariable analysis (any complication: OR=1.65, 95%CI=1.08-2.26, P=0.018; UTI: OR=2.62, 95%CI=1.07-3.21, P=0.029; AUR: OR=4.51, 95%CI=1.93-10.54, P=0.001; hematospermia: OR=1.85, 95%CI=1.07-3.21, P=0.029; hematuria: OR=1.19, 95%CI=0.74-1.93, P=0.472).

Conclusion: In men undergoing repeat prostate biopsy, a previous biopsy-related complication and the type of complication were associated with lower compliance with re-biopsy schemes. Patients experiencing biopsy-related complications are ideal candidates to receive interventions regarding the importance of prostate re-biopsy to prevent noncompliance.

Introduction:

Transrectal ultrasound (TRUS)-guided prostate biopsy remains the most common procedure to diagnose prostate cancer.[1] Despite its reasonable accuracy, up to 30% of first prostate biopsies are negative, and between 18% and 32% of patients are diagnosed with prostate cancer on a repeat biopsy.[2,3,4] Unfortunately, a considerable number of patients are noncompliant with repeat biopsy schemes. Indeed, a recent clinical trial showed that 22% of patients did not comply with a study-mandated repeat prostate biopsy.[5] While the causes for prostate biopsy noncompliance are not entirely understood, African-American race, and medical care at a low-volume center were associated with higher risk of repeat biopsy noncompliance.[5]

Although TRUS-guided prostate biopsy is a generally safe procedure, it is associated with potential complications, including hematuria, urinary tract infection (UTI), acute urinary retention (AUR), and hematospermia.[5-9] While the risk of such complications is low, with occurrences between 0.4% and 5.2%, the effect of these complications on patient compliance to future prostate biopsies has not been studied in earnest.[6,7,9,10] A study of patients with prostate cancer in an active surveillance protocol suggested that prior prostate biopsy complication may be associated with future re-biopsy noncompliance.[9] However, it remains unknown whether complications and type of complications affect compliance with re-biopsy schemes among men without prostate cancer who are not on an active surveillance program. Thus, we sought to evaluate whether previous prostate biopsy-related complications and the type of complication experienced were associated with repeat prostate biopsy compliance in a clinical trial with study-mandated systematic prostate biopsies. We hypothesize that prostate biopsy-related complications will be associated with higher repeat biopsy noncompliance.

Materials and Methods:

Study Population

Data for the present study was obtained from the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial, which had inclusion criteria of: men aged 50 to 75 years with a serum prostate-specific antigen (PSA) level ≥ 2.5 or 3.0ng/mL according to age (50-60 and 60-75 years, respectively) but ≤ 10 ng/mL, and one single negative prostate biopsy (6 to 12 cores) within

6 months of enrollment.[11] Exclusion criteria were: history of prostate cancer, high-grade intraepithelial neoplasia, atypical small acinar proliferation, previous prostate surgery, prostate volume > 80 mL, had an International Prostate Symptom Score (IPSS) ≥ 25 (≥ 20 for men taking alpha-blockers) or were previously on finasteride or dutasteride. During the study interval patients underwent prostate biopsy at 2 and 4 years. The systematically recorded biopsy-related complications were chosen a-priori and included: hematuria within 7 days, UTI within 14 days, AUR within 7 days, and hematospermia within 90 days from biopsy. Hematuria and hematospermia complications were defined as the presence of blood in the urine or semen, respectively, considered by the treating physician to be more severe than expected. UTI was defined as the presence of urinary symptoms compatible with UTI and the prescription of antibiotics by the treating physician. A positive urine culture was not required for the diagnosis of UTI. Hospital admission rates were obtained to assess severity of UTI complication. AUR was defined as the inability to urinate requiring bladder catheterization. Patient compliance with 4-year repeat prostate biopsy was recorded. Covariates were measured at the time of the 2-year biopsy unless otherwise specified. The protocol was approved by the institutional review board at each research site, and all participants provided written informed consent. A total of 6,490 men underwent a 2-year prostate biopsy. Of these, 5,087 (78.4%) were eligible for the 4-year biopsy. Reason for ineligibility for the 4-year biopsy were: 663 (10.2%) diagnosis of prostate cancer, 219 (3.4%) consent withdrawal, 146 (2.2%) adverse event or side-effect related to the drug in study (dutasteride), 59 (0.9%) loss of follow up, 19 (0.3%) protocol violation, and 297 (4.6%) other or unknown. Of the 5,087 eligible subjects for the 4-year biopsy, we excluded 148 (2.3%) due to missing data in at least one of the other covariates (see below). This resulted in a final study sample of 4,939 (76.1%) subjects (Figure 1).

Statistical Analysis

Results are presented as means and standard deviations (SDs) for continuous variables and counts and percentages for categorical data. The primary aim of this study was to evaluate the association of any prostate biopsy-related complication at the 2-year biopsy with patient noncompliance with the 4-year re-biopsy. Comparisons of baseline characteristics between

subjects who experienced prostate biopsy-related complication at the 2-year biopsy and those who did not were done with chi-square test for categorical variables and Student *t* test for continuous data. Logistic regression was used to test the association between 2-year biopsy complications and noncompliance with the 4-year repeat prostate biopsy in both unadjusted and adjusted models, controlling for baseline covariates including age (continuous, in years), race (White, non-White), body-mass index (BMI, continuous, in kg/m^2), family history of PCa (yes or no), digital rectal exam (DRE, coded as normal or abnormal), prostate volume (PV, continuous, in cm^3), PSA (continuous, in ng/mL), peak flow (PF, continuous, in ml/s), postvoid residual (PVR, continuous, in mL), center volume (continuous), number of cores sampled at the 2-year biopsy, geographic region (North America, Europe or other), diabetes mellitus (present or absent), and treatment arm (dutasteride or placebo). Results of logistic regression analyses are presented as odds ratios (ORs), 95% confidence intervals (CIs) and P values. The secondary aim of this study is to evaluate the association of the following specific prostate biopsy-related complications at the 2-year prostate biopsy (hematuria, UTI, AUR and hematospermia) with patient noncompliance at the 4-year re-biopsy. This was analyzed as described for the primary aim. We performed two sensitivity analyses: first, including IPSS and CPSI (both continuous) data (N=3,231) in multivariable models; second, only including subjects with PSA < 4 ng/mL. All statistical analyses were two-tailed and performed using Stata 12.0 (StataCorp, College Station, TX). A $P < 0.05$ was considered statistically significant.

Results:

Among the 4,939 subjects included in the study, the mean age was 64.5 years (SD=5.9), PSA level was 4.9 ng/mL (SD=6.7), and prostate volume was 46.0 cm^3 (SD=21.4). On average, study subjects were slightly overweight with a mean BMI of 27.4 kg/m^2 (SD=3.9); while prevalence of diabetes mellitus was 8.1%. Most subjects (91.9%) were white, the majority were from Europe (61.1%) and North America (24.4%, Table 1).

A total of 260 (5.3%) subjects experienced at least one of the recorded complications (UTI, AUR, hematuria and hematospermia) after the 2-year prostate biopsy. The leading complication was hematuria in 180 (3.6%) patients, followed by hematospermia, UTI and urinary retention in 102 (2.1%), 36 (0.7%), and 26 (0.5%) patients, respectively. Of the patients who experienced a

UTI, there were 9 (25%) required hospital admission. Table 1 shows patient characteristics by 2-year prostate biopsy complications. Subjects who experienced a complication had significantly larger prostate volumes, higher post void residual volume, they were more likely to live in North America or Europe and to be in the placebo group compared to those who did not experience any complications (all $P < 0.05$). The other characteristics evaluated including age, PSA levels, BMI, PV, IPSS, CPSI, PVR, PF, total cores sampled, center volume, DRE, and DM were comparable between complication groups.

Overall, a total of 474 (9.6%) of the subjects were noncompliant with the 4-year prostate re-biopsy. Among subjects who had a complication, 36 (13.9%) were noncompliant with the 4-year biopsy compared to 438 (9.4%) among those who experienced no complications. In univariable analysis, any previous complication (OR=1.56, 95%CI=1.08-2.24, P=0.018), UTI (OR=2.72, 95%CI=1.23-6.00, P=0.013), AUR (OR=4.24, 95%CI=1.83-9.81, P=0.016) and hematospermia (OR=1.78, 95%CI=1.03-3.06, P=0.037) were significantly associated with higher risk of re-biopsy noncompliance. Hematuria was not associated with repeat biopsy noncompliance (OR=1.19, 95%CI=0.74-1.91, P=0.483). Comparable results were observed in multivariable analysis, with a higher risk of re-biopsy noncompliance observed in patients with any complication (OR=1.65, 95%CI=1.08-2.26, P=0.018). Specifically, UTI (OR=2.62, 95%CI=1.18-5.82, P=0.018), AUR (OR=4.51, 95%CI=1.93-10.54, P=0.001) and hematospermia (OR=1.85, 95%C =1.07-3.21, P=0.029) were associated with higher risk of re-biopsy noncompliance; while hematuria was not associated with repeat biopsy noncompliance (OR=1.19, 95%CI=0.74-1.93, P=0.472). In two sensitivity analysis, including IPSS and CPSI to multivariable models and restricting to patients with PSA < 4 ng/mL, the results were virtually unchanged (data not shown).

Discussion:

Patient noncompliance with prostate biopsies may be linked to fear of pain, discomfort or other biopsy-related complications including hematuria, UTI, AUR and hematospermia. A negative prior experience with prostate biopsy, such as complications may affect patient compliance with re-biopsy schemes. However, there are no studies evaluating how complications in a prior prostate biopsy affects patient adherence to re-biopsy schemes amongst patients without prostate cancer who are not in an active surveillance protocol. Thus, we evaluated

whether previous prostate biopsy-related complications and the type of complication were associated with repeat prostate biopsy compliance in a clinical trial with study-mandated systematic biopsies. We found that any complication at the 2-year biopsy was significantly associated with re-biopsy noncompliance at the study mandated 4-year re-biopsy. In addition, UTI, AUR and hematospermia were particularly associated with noncompliance with re-biopsy.

Although the causes for noncompliance with prostate biopsy are not entirely clear, several studies have shown the noncompliance rate varies from 22% to 45%.[5,9] For example, Fischer *et al.* demonstrated that 22% of patients were non-compliant with study mandated prostate re-biopsy.[5] In addition, they found North American men, African-American race and treatment at low-volume centers were associated with higher risk of re-biopsy noncompliance. Another study by Bokhorst *et al.* focused on patients with diagnosed prostate cancer who were undergoing an active surveillance protocol and experienced previous complications including: infection, hematuria, hematospermia and pain.[9] An average of 30% of patients were non-compliant with prostate re-biopsies.[9] Noncompliance with re-biopsy increased from 19% in the first year to 40% in the fourth year and 47% in the seventh year.[9] They concluded that patients who experienced any complication were more likely to be noncompliant with re-biopsies as part of the active surveillance protocol.[9] Although the causes for noncompliance were not completely determined, the authors indicated that repeat biopsies put a substantial strain on men.[17,18] Similarly, we found that, among men without prostate cancer undergoing repeat prostate biopsy for cancer detection, prostate biopsy-related complications and the type of complication were associated with decreased re-biopsy compliance. Moreover, in another study of patients undergoing biopsy in a prostate screening program, roughly 65% of patients reported the procedure as unpleasant with over half experiencing moderate pain following the procedure.[19] Of those patients, approximately 25% responded that they would be unwilling to undergo a repeat biopsy if needed.[19] Although it is plausible that other factors such as logistics and costs could interfere with re-biopsy compliance, our results and previous studies in this subject suggest a prior negative experience with prostate biopsy, such as pain or complications, is likely the main reason for re-biopsy noncompliance.

Given noncompliance to prostate biopsy can lead to missed or delayed diagnosis of cancer, efforts to maximize patient adherence to biopsy schemes are important. Our results indicate that men who experienced a biopsy-related complication are ideal targets of such initiatives given they are at a higher risk for noncompliance. Recent studies on improving patient compliance with treatment strategies emphasize the role of a strong doctor-patient relationship and patient education for improving compliance outcomes.[21] Physicians should focus their efforts on improving the quality of the doctor-patient relationship and educate their patients on the importance of medical interventions such as a prostate biopsy, the possible complications and the rationale for why the benefits outweigh the risks.[20,21] By doing so, patients will be more educated to make a well informed decision regarding the importance of adhering to their prostate biopsy especially in cases where previous complications are experienced. These recommendations are similar to many studies that have attempted to find a solution for improving patient adherence to medication regiments.[22] Patients that previously underwent an educational program regarding treatment of their disease were significantly more likely to adhere to their medication regiments.[22] Therefore by utilizing effective communication strategies and educating patients on the risk-benefit ratio, urologists may mitigate the risk for noncompliance, thus preventing potential missed prostate cancer diagnoses.

Our study has several strengths including a large multicentric sample with detailed biopsy complication data. However, it has several limitations. First, hematuria and hematospermia did not have a strict definition and were at the discretion of the treating physician. Second, we did not have data on patient counseling prior to prostate biopsy. Third, UTI diagnosis was not based on a positive urine culture but rather on a patient's symptoms and the initiation of antibiotics which, in some way, mimics the experience of a true UTI. Fourth, per the study design subjects were required to have re-biopsies at year 4 regardless of PSA and some men had PSA levels at the time of re-biopsy below the typical threshold for prostate biopsy. It is plausible that the perceived low prostate cancer risk due to low PSA levels may have influenced re-biopsy compliance, although our results restricting to patients with PSA <4ng/mL do not support such a hypothesis. Fifth, it is unclear how our results apply to patients outside of a clinical trial or in other re-biopsy schemes such as active surveillance for prostate cancer since patients knew they

would be undergoing repeat biopsies when they enrolled in the study and they did not have the diagnosis of cancer. Sixth, we were unable to analyze other complications such as rectal bleeding and pain as these were not systematically recorded. Seventh, the number of complications, including type and severity, was relatively small which limits our statistical power and raises the possibility of overfitting. Lastly, we were unable to evaluate the cause for noncompliance given our sample was not surveyed for the cause of noncompliance and their overall experience with prostate biopsy.

Conclusion:

In conclusion, among subjects in a clinical trial with study-mandated prostate biopsies, those who experience a biopsy-related complication were more likely to be noncompliant with a prostate re-biopsy. Specifically, UTI, AUR and hematospermia were associated with significantly higher noncompliance rates. Effective interventions targeting high-risk patients for prostate biopsy noncompliance may prevent prostate cancers from going undiagnosed.

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Table 1: Baseline characteristics of study participants by complications at 2-year prostate biopsy

	All comers	Complications		
		No	Yes	P value
N (%)	4,939	4,679(94.7%)	260(5.3%)	-
Age in years, mean (SD)	64.5 (5.9)	64.5 (6.0)	64.3 (5.9)	0.723
PSA, mean (SD)	4.9 (6.7)	4.9 (6.9)	4.6 (3.3)	0.525
BMI, mean(SD)	27.4 (3.9)	27.4 (3.9)	27.4 (3.6)	0.840
PV, mean(SD)	46.0 (21.4)	45.8 (21.5)	48.6 (20.5)	0.041
PVR, mean (SD)	47.1 (48.4)	46.5 (48.3)	58.1 (50.0)	0.002
PF, mean (SD)	14.6 (18.0)	14.6 (18.4)	14.5 (7.8)	0.954
Total cores sampled, mean (SD)	10.1 (0.5)	10.1 (0.5)	10.1 (0.3)	0.733
Center volume, mean (SD)	40.8 (43.3)	40.8 (43.7)	40.7 (35.6)	0.990
DRE, n (%)				0.231
Normal or enlarged	4,775 (96.7%)	4,527 (94.8%)	248 (5.2%)	
Abnormal	164 (3.3%)	152 (92.7%)	12 (7.3%)	
Race, n (%)				0.174
White	4,537 (91.9%)	4,304 (94.9%)	233 (5.1%)	
Other	402 (8.1%)	375 (93.3%)	27 (6.7%)	
Treatment arm, n (%)				0.001
Placebo	2,428 (49.2%)	2,275 (93.7%)	153 (6.3%)	
Dutasteride	2,511 (50.8%)	2,404 (95.7%)	107 (4.3%)	
Region, n (%)				<0.001
North America	1,204 (24.4%)	1,099 (91.3%)	105 (8.7%)	
Europe	3,018 (61.1%)	2,897 (96.0%)	121 (4.0%)	
Other	717 (14.5%)	683 (95.3%)	34 (4.7%)	
DM, n (%)				0.509
Yes	402 (8.1%)	378 (94.0%)	24 (6.0%)	
No	4,536 (91.9%)	4,300 (94.8%)	236 (5.2%)	
Any biopsy complication, n (%)				
Yes	260 (5.3%)			
No	4,679 (94.7%)			
Hematuria, n (%)				
Yes	180 (3.6%)			
No	4,759 (96.4%)			
UTI, n (%)				
Yes	36 (0.7%)			
No	4,903 (99.3%)			
AUR, n (%)				
Yes	26 (0.5%)			
No	4,913 (99.5%)			
Hematospermia, n (%)				
Yes	102 (2.1%)			
No	4,837 (97.9%)			

PSA=Prostate Specific Antigen (ng/mL); BMI=Body Mass Index (kg/m^2); PV=Prostate Volume (cm^3); PVR=Post Void Residual (mL); PF=Peak Flow (mL/sec); DRE=Digital Rectal Exam; DM=Diabetes Mellitus; UTI=Urinary Tract Infection

Table 2: Prostate re-biopsy compliance by history of biopsy-related complication

Complication		Re-biopsy compliance		Univariable			Multivariable**		
	N	No	Yes	OR	95% CI	P	OR	95% CI	P
		N (%)	N (%)						
None	4,679	438 (9.4%)	4,241 (90.6%)	*ref.*	--	--	*ref.*	--	--
Any	260	36 (13.9%)	224(86.2%)	1.56	1.08-2.24	0.018	1.56	1.08-2.26	0.018
Hematuria	180	20 (11.1%)	160 (88.9%)	1.19	0.74-1.91	0.483	1.19	0.74-1.93	0.472
UTI	36	8 (22.2%)	28 (77.8%)	2.72	1.23-6.00	0.013	2.62	1.18-5.82	0.018
AUR	26	8 (30.8%)	18 (69.2%)	4.24	1.83-9.81	0.016	4.51	1.93-10.54	0.001
Hematospermia	102	16 (15.7%)	86 (84.3%)	1.78	1.03-3.06	0.037	1.85	1.07-3.21	0.029

AUR: acute urinary retention, CI: confidence interval, OR: odds ratio, UTI: urinary tract infection

**Adjusted for age, race, family history of prostate cancer, body-mass index, digital rectal exam, prostate volume, prostate-specific antigen, IPSS score, CPSI score, peak flow, total cores sampled, geographic region, diabetes mellitus, and treatment arm (dutasteride or placebo)

Figure 1: Flow chart of inclusion and exclusion criteria for this study: