Timing of Adverse Prostate Cancer Reclassification on First Surveillance Biopsy: Results from the Canary Prostate Cancer Active Surveillance Study

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Abbreviations and Acronyms

AS = active surveillance

BMI = body mass index

CAPRA = Cancer of the Prostate Risk Assessment

DRE = digital rectal examination

MRI = magnetic resonance imaging

NCCN® = National Comprehensive Cancer Network®

PASS = Prostate Cancer Active Surveillance Study

PCa = prostate cancer

PSA = prostate specific antigen

PSAD = PSA density

TRUS = transrectal ultrasound

Purpose: During active surveillance for localized prostate cancer, the timing of the first surveillance biopsy varies. We analyzed the Canary PASS (Prostate Cancer Active Surveillance Study) to determine biopsy timing influence on rates of prostate cancer adverse reclassification at the first active surveillance biopsy.

Materials and Methods: Of 1,085 participants in PASS, 421 had fewer than 34% of cores involved with cancer and Gleason sum 6 or less, and thereafter underwent on-study active surveillance biopsy. Reclassification was defined as an increase in Gleason sum and/or 34% or more of cores with prostate cancer. First active surveillance biopsy reclassification rates were categorized as less than 8, 8 to 13 and greater than 13 months after diagnosis. Multivariable logistic regression determined association between reclassification and first biopsy timing.

Results: Of 421 men, 89 (21.1%) experienced reclassification at the first active surveillance biopsy. Median time from prostate cancer diagnosis to first active surveillance biopsy was 11 months (IQR 7.8–13.8). Reclassification rates at less than 8, 8 to 13 and greater than 13 months were 24%, 19% and 22% ($p = 0.65$). On multivariable analysis, compared to men biopsied at less than 8 months the OR of reclassification at 8 to 13 and greater than 13 months were 0.88 (95% CI 0.5,1.6) and 0.95 (95% CI 0.5,1.9), respectively. Prostate specific antigen density 0.15 or greater (referent less than 0.15, OR 1.9, 95% CI 1.1, 4.1) and body mass index 35 kg/m^2 or greater (referent less than 25 kg/m^2, OR 2.4, 95% CI 1.1,5.7) were associated with increased odds of reclassification.

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Conclusions: Timing of the first active surveillance biopsy was not associated with increased adverse reclassification but prostate specific antigen density and body mass index were. In low risk patients on active surveillance, it may be reasonable to perform the first active surveillance biopsy at a later time, reducing the overall cost and morbidity of active surveillance.

Key Words: prostatic neoplasms, prostate specific antigen, body mass index, biopsy, watchful waiting

WITH the advent of PSA testing and subsequent biopsy, up to 80% of diagnosed prostate cancer may be indolent, posing a small risk of morbidity or mortality during the patient lifetime.[1,2] Nonetheless, contemporary data suggest that most patients with NCCN low/very low risk PCa[3] receive definitive therapy, despite a lack of evidence of improved survival or reduced morbidity.[4,5]

Treatment with AS in patients with low risk PCa may reduce the risk of overtreatment by delaying therapy and treating only those in whom clinically significant malignancy develops. Patients on AS undergo monitoring with PSA measurements, DREs and prostate biopsies. AS has limited data supporting the superiority of any specific followup schedule.[6]

The decision to abandon AS and initiate therapy is usually based on factors including changes in PSA, DRE and biopsy characteristics as well as fatigue/anxiety related to surveillance[7] or uncertainty that the cancer is truly favorable risk.[7] Patient and provider concerns regarding the accuracy of available monitoring methods as well as missing a curative treatment window may contribute to decisions to abandon AS and initiate treatment.

Recognizing that systematic TRUS guided biopsy can miss tumors of greater biological potential, the first biopsy performed after entering into an AS program, also referred to as confirmatory biopsy, is almost uniformly recommended.[8] There is no consensus on when to perform such a first/confirmatory biopsy. Most protocols suggest the first AS biopsy 6 to 12 months after diagnostic biopsy.[9–11] As the "required" periodic biopsy for patients on AS are a drawback to surveillance and a source of patient dissatisfaction and morbidity, optimal timing for even the first AS biopsy is important for greater acceptance of surveillance.

We previously reported 5-year outcomes in the Canary PASS.[12] The current study was designed to specifically address optimal timing of the first AS biopsy. We sought to define rates of adverse reclassification (thus, reclassification) on the first AS biopsy, stratified by the timing of the first AS biopsy. We hypothesized that among men undergoing a first AS biopsy in the recommended time frame of PASS, there would be no significant association between reclassification and timing. Additionally, we sought to identify factors associated with first AS biopsy reclassification.

METHODS

The PASS protocol (ClinicalTrials.gov NCT00756665) was approved by institutional review boards at Stanford University, University of British Columbia, University of California-San Francisco, University of Texas Health Sciences Center San Antonio, University of Washington, Veterans Affairs Puget Sound Health Care System and Fred Hutchinson Cancer Research Center (the coordinating center). It opened for enrollment in 2008.[13] Subsequently, the protocol was approved and enrollment opened at Beth Israel Deaconess Medical Center, Eastern Virginia Medical School and University of Michigan. All men provided informed written consent. Eligibility criteria for PASS have been described previously.[12] For this study, data were frozen on March 25, 2014, when 1,085 men were enrolled.

We selected a subgroup of PASS for analysis with at least a diagnostic biopsy as well as an on-study first AS biopsy. We excluded men diagnosed by transurethral resection of the prostate and those with fewer than 10 cores on diagnostic biopsy, a diagnostic biopsy with 34% or more cores involved with cancer, a greatest Gleason score of 4 or greater, or PSA greater than 20 ng/ml. Reclassification was defined as a first AS biopsy with any Gleason pattern 4 or greater, or 34% or more cores involved with cancer. All cases were clinical stage cT2c or less.

The PASS protocol recommends performing the first AS biopsy 6 to 12 months after diagnosis. There is heterogeneity, resulting in a first AS biopsy greater than 12 months after diagnosis for some men. Biopsies were all TRUS guided with 10 or more cores. MRI fusion technology was not available because of the current data freeze.

PASS allows for minor regional practice variation. Thus, there is no standard biopsy protocol. The overwhelming majority of providers obtain 12 or more cores. First AS biopsy timing was categorized based approximately on tertiles, reflecting practice in PASS, including fewer than 8, 8 to 13 and greater than 13 months after diagnostic biopsy. Given the lack of consensus on first surveillance biopsy timing, these 3 intervals are potentially meaningful cutoff points for early, intermediate and deferred first AS biopsy, respectively.

Multivariate logistic regression was used to determine associations between reclassification, and first AS biopsy timing and other covariates. For this analysis, biopsy specimens were evaluated for Gleason score by genitourinary pathologists at the PASS sites using the 2005 WHO/ISUP (International Society of Urologic

Pathologists) modified Gleason system.[14] Central pathology review was not performed.

De-identified demographic, clinical and pathological data are centrally maintained at Fred Hutchinson Cancer Research Center and managed at the NCI (National Cancer Institute) Early Detection Research Network Data Management and Coordination Center. A collaboration agreement governing study conduct and data use was executed at participating institutions.

The primary exposure was timing of the first AS biopsy. The primary outcome was the rate of reclassification on the first AS biopsy, defined as any Gleason pattern 4 or greater, or an increase to 34% or more cores with cancer on the first AS biopsy. Descriptive data are also provided on subtypes of reclassification, given possible gradations in prognosis (ie, primary Gleason pattern compared to secondary Gleason pattern reclassification and combined grade/volume reclassification). PSA was not used in the definition of reclassification.[15]

Covariates for baseline cohort description and multivariable modeling were selected a priori based on their established relationship with PCa prognosis. These covariates included demographics (age, race and ethnicity), comorbidities (family history and BMI in kg/m^2) and oncologic/pathological features (diagnostic PSA, diagnostic PSAD, DRE characteristics, NCCN risk stratum,[3] CAPRA score,[16] clinical stage classification, diagnostic TRUS volume and location of diagnostic biopsy as study site or referred).

Statistical Analysis

Continuous variables were categorized as shown in table 1. Multivariable logistic regression was used to model factors associated with adverse reclassification on the first AS biopsy. Both unadjusted and multivariable models were applied. All a priori covariates were included in the unadjusted model. The multivariable model was then backward selected in stepwise fashion with a preset significance level for inclusion of $p < 0.2$ to minimize overfitting the model, which included the variables in table 2. The Hosmer-Lemeshow goodness of fit test was used to assess model specification[17] and the concordance statistic (AUC) was calculated to determine the predictive accuracy of the model.[18]

Several sensitivity analyses were done to assess the selection of cutoff points for continuous variables. Both PSA at diagnosis and the interval from diagnostic biopsy to first surveillance biopsy were assessed as continuous variables. We also verified that trends observed for the entire study group were consistent among the presumed highest risk reclassification subgroups (primary Gleason reclassification with/without volume reclassification). None of the sensitivity analyses resulted in significantly different associations between exposures and reclassification compared to the primary analysis. Statistical analysis was performed using SAS®, version 9.3 and STATA®, version 13.

RESULTS

After exclusions, 421 men were eligible with median followup of 30 months (range 3 to 71) and a median time to first AS biopsy of 11 months (range 4 to 28). For the tertile subgroups, median time to first AS biopsy was 6.3 (IQR 5.8–7.7), 11.5 (IQR 10.6–12.1) and 15.4 months (IQR 13.6–21.5), respectively. Patient characteristics are given in table 1, stratified by timing of the first AS biopsy.

Overall, 89 men (21.1%) were reclassified at the first AS biopsy. There was no difference in the reclassification rate whether the first AS biopsy was done at less than 8 months (23.5% of cases), 8 to 13 months (19.2%) or greater than 13 months (21.7%) (chi-square $p = 0.65$). Additionally, 144 men (34%) had no cancer identified on the first AS biopsy.

Most participants were diagnosed after age 55 years, racially identified as white, and had a negative family history and BMI less than 30 kg/m^2. Approximately 6% of men (26 of 421) were at NCCN intermediate risk or had a CAPRA score greater than 2. The few men who were at intermediate risk were so classified based on PSA greater than 10 ng/ml.

On baseline chi-square comparison, the 3 biopsy timing groups were well balanced except that men diagnosed at a community center and then referred to PASS were more likely to undergo the first AS biopsy during the less than 8-month interval (table 1).

Given the presumed different prognosis for reclassification of the primary Gleason pattern compared to the secondary Gleason pattern, we report reasons for reclassification (table 3). Grade reclassification affected 77 of 89 reclassified men (86.5%). The most common pattern of reclassification in 43 of 89 patients (48.3%) was to primary Gleason pattern 3 with secondary pattern 4 or greater and no increase to 34% or more core involvement. Concurrent volume and grade reclassification affected 7 of 89 men (7.8%), that is both primary Gleason 4 and volume increase to 34% or more core involvement. Among the men reclassified for an increase in secondary Gleason pattern, 2 had secondary pattern 5 but none had primary pattern 5. Importantly, we verified that among the 7 of 89 men with primary Gleason 4 and a volume increase, there was no difference in the rate of reclassification at the less than 8, 8 to 13 or greater than 13-month biopsy intervals (chi-square $p = 0.94$). Similarly, among the 19 of 89 men reclassified with primary pattern 4, there was no difference based on the tertile of timing ($p = 0.60$).

Table 4 shows the cohort stratified by reclassification status. BMI and PSAD were associated with reclassification on baseline chi-square analysis. On unadjusted logistic regression (table 2), BMI greater than 35 kg/m^2 (referent less than 25 kg/m^2) and PSAD 0.15 ng or greater (referent less than 0.15

Table 1. *Baseline characteristics of Canary PASS subcohort stratified by tertiles from diagnostic biopsy to first active surveillance biopsy*

Subgroup	No. Pts	No. Less Than 8 Mos (%)	No. 8—13 Mos (%)	No. Greater Than 13 Mos (%)	p Value (chi-square test)
Overall		119 (28.3)	173 (41.1)	129 (30.6)	—
			Outcome		
Reclassified on 1st AS biopsy:*					
Gleason	77	25 (21.0)	25 (14.5)	27 (20.9)	0.29
Vol	34	7 (5.9)	15 (8.7)	12 (9.3)	0.58
Either	89	28 (23.5)	33 (19.2)	28 (21.7)	0.71
			Demographics		
Age at diagnosis:					0.43
Less than 55	61	15 (12.6)	26 (15.0)	20 (15.5)	
55—64.9	190	53 (44.5)	86 (49.7)	51 (39.5)	
65 or Greater	170	51 (42.9)	61 (35.3)	58 (45.0)	
Race:					0.49
White	382	106 (89.1)	157 (90.8)	119 (92.3)	
Black	19	8 (6.7)	5 (2.9)	6 (4.6)	
Other	20	5 (4.2)	11 (6.3)	4 (3.1)	
Ethnicity:					0.09
Hispanic	17	2 (1.7)	6 (3.5)	9 (7.0)	
NonHispanic	404	117 (98.3)	167 (96.5)	120 (93.0)	
			Clinical factors		
Family history:					0.42
Pos	103	35 (29.4)	43 (24.8)	25 (19.4)	
Neg	300	79 (66.4)	124 (71.7)	97 (75.2)	
Missing	18	5 (4.2)	6 (3.5)	7 (5.4)	
BMI (kg/m^2):					0.18
Less than 25	100	25 (21.0)	49 (28.3)	26 (20.2)	
25—29.9	215	60 (50.4)	88 (50.9)	67 (51.9)	
30—34.9	71	26 (21.9)	25 (14.4)	20 (15.5)	
35 or Greater	35	8 (6.7)	11 (6.4)	16 (12.4)	
			Ca + biopsy related covariates		
PSA (ng/ml):					0.26
Less than 4	125	29 (24.4)	58 (33.5)	38 (29.4)	
4—10	270	79 (66.4)	105 (60.7)	86 (66.7)	
11—20	37	11 (9.2)	10 (5.8)	5 (3.9)	
PSAD (ng):					0.31
Less than 0.15	291	77 (64.7)	119 (68.8)	95 (73.6)	
0.15 or Greater	130	42 (35.3)	54 (31.2)	34 (26.3)	
DRE:†					0.18
Benign	358	106 (90.6)	139 (83.7)	113 (89.0)	
Suspicious	52	11 (9.4)	27 (16.3)	14 (11.0)	
NCCN risk:					0.20
Low/very low	395	108 (90.8)	163 (94.2)	124 (96.1)	
Intermediate	26	11 (9.2)	10 (5.8)	5 (3.9)	
CAPRA score:‡					0.61
0	19	4 (3.4)	7 (4.0)	8 (6.2)	
1	291	78 (65.5)	124 (71.7)	89 (69.0)	
2	87	27 (22.7)	33 (19.1)	27 (20.9)	
3	24	10 (8.4)	9 (5.2)	5 (3.9)	
TRUS prostate vol (cm^3):					0.16
Less than 30	112	23 (19.3)	50 (28.9)	39 (30.2)	
30—50	171	56 (47.1)	71 (41.0)	44 (34.1)	
Greater than 50	138	40 (33.6)	52 (30.1)	46 (35.7)	
Diagnostic biopsy site:					<0.01
Study center	162	31 (26.1)	82 (47.4)	49 (38.0)	
Off site	259	88 (73.9)	91 (53.6)	80 (62.0)	

* Patients with first AS biopsy during that time.
† Missing data on 10 men.
‡ No score greater than 3.

ng) were associated with reclassification. In a multivariable model adjusting for all covariates, BMI greater than 35 kg/m^2 was associated with a greater than threefold increase in the odds of reclassification and PSAD 0.15 ng or greater was associated with a twofold increase in the odds of

Table 2. *Unadjusted and backward selected multivariable logistic regression models of association between reclassification on first active surveillance biopsy and clinical variables*

	Unadjusted OR (95% CI)	Multivariable OR (95% CI)
1st AS biopsy timing (mos):		
Less than 8	Referent	Referent
8—13	0.80 (0.45—1.40)	0.78 (0.43—1.41)
Greater than 13	0.91 (0.53—1.63)	0.89 (0.47—1.67)
Age at diagnosis:		Not included
Less than 55	Referent	
55—64.9	1.04 (0.53—2.28)	
65 or Greater	1.17 (0.56—2.41)	
Race:		Not included
White	Referent	
Black	1.70 (0.79—5.26)	
Other	0.67 (0.19—2.33)	
Ethnicity:		Not included
Hispanic	0.48 (0.11—2.14)	
NonHispanic	Referent	
Family history:		Not included
Pos	0.79 (0.44—1.39)	
Neg	Referent	
Missing	1.00 (0.32—3.13)	
BMI (kg/m^2):		
Less than 25	Referent	Referent
25—29.9	0.69 (0.39—1.24)	0.72 (0.40—1.30)
30—34.9	0.64 (0.30—1.39)	0.72 (0.33—1.59)
35 or Greater	3.00 (1.50—6.21)*	2.67 (1.14—6.21)*
PSA (ng/ml):		
Less than 4	Referent	Referent
4—10	1.56 (0.90—2.73)	1.39 (0.74—2.63)
10—20	2.21 (0.85—5.74)	1.61 (0.47—5.52)
PSAD (ng):		
Less than 0.15	Referent	Referent
0.15 or Greater	2.05 (1.31—3.48)*	1.96 (1.12—4.13)*
DRE:		Not included
Benign/enlarged	Referent	
Suspicious	1.39 (0.71—2.70)	
NCCN risk:		Not included
Low/very low	Referent	
Intermediate	1.41 (0.57—3.46)	
CAPRA score:		Not included
0	Referent	
1	5.18 (0.68—39.5)	
2	4.06 (0.50—32.1)	
3	8.47 (0.96—75.1)	
TRUS prostate vol (cm^3):		
Less than 30	Referent	Referent
30—50	0.95 (0.54—1.65)	1.11 (0.57—2.15)
Greater than 50	0.53 (0.28—1.09)	0.57 (0.25—1.28)
Diagnostic biopsy site:		Not included
Study center	1.08 (0.67—1.73)	
Off site	Referent	

* Statistically significant.

reclassification compared to the respective referent groups (table 2). Results were no different when repeating these models with time to first surveillance biopsy as a continuous variable (data not shown). When using both time to biopsy and PSA as continuous variables, there were no statistically significant associations with adverse reclassification on the first AS biopsy (data not shown). The Hosmer-Lemeshow $p = 0.65$ of the final model led us to reject the hypothesis that the model was overfit. The AUC of the model was 0.67.

Table 3. *Reasons for adverse prostate cancer Gleason grade reclassification in 89 men in Canary PASS who were reclassified at first active surveillance biopsy*

	No. Vol Reclassification (%)*	
Grade Reclassification	No	Yes
No (Gleason pattern 3 + 3)	Not applicable	12 (13.5)
Yes (Gleason pattern):		
3 + 4	43 (48.3)	15 (16.9)
4 + 3	12 (13.5)	7 (7.8)

* Cancer involvement in 34% or more of cores in reclassified men.

DISCUSSION

The most important result of this analysis is that the rate of reclassification was not affected by the first AS biopsy interval. In this study, the overall risk of reclassification on the first AS biopsy was 21% (18% if only grade is considered). Importantly, however, PSAD and BMI were associated with a significant increase in the risk of reclassification. As would be expected, the most common pathological finding leading to reclassification was an increase to Gleason grade 3 + 4 with or without a concomitant increase to 34% or more core involvement.

Our finding of a 21% rate of reclassification at first AS biopsy is consistent with other series, with rates ranging from 15% to 42%.[19,20] Additionally, in patients at low risk on AS, median time to reclassification was reported to be around 2 years,[21] resulting in a clinical dilemma between detecting occult aggressive disease and making AS more cost-effective/tolerable. The rate of reclassification was not significantly affected by time to the first AS biopsy within the range of times to biopsy observed in this study. This supports the notion that reclassification of the majority of men was due to sampling error in the diagnostic biopsy rather than to biological disease progression.

During initial counseling regarding the treatment of low risk, localized PCa, men should be informed that approximately 1 of 5 men who initially elect surveillance will have more aggressive disease on the first surveillance biopsy. The timing of AS biopsy, when only the low risk group is studied, appears to have little relationship with reclassification. As such, it would appear that patients and their physicians have some flexibility regarding the timing of the first AS biopsy. Given that the observed reclassifications included no primary pattern 5 and rare primary pattern 4, the theoretical risk of interim metastasis is thought to be acceptably low.

It is also important to recognize that reclassification, which is most commonly an increase in Gleason score from 3 + 3 on initial biopsy to 3 + 4 on subsequent biopsy, does not require or always result in a change to active treatment. A growing

Table 4. *Canary PASS cohort reclassification status at first active surveillance biopsy stratified by clinically relevant variables*

Substratum	No. Pts	No. Not Reclassified (%)	No. Reclassified (%)	p Value (chi-square test)
Overall	—	332 (78.9)	89 (21.1)	—
		Outcomes		
1st AS biopsy timing (mos):				0.65
Less than 8	119	91 (27.4)	28 (31.5)	
8—13	173	140 (42.2)	33 (37.1)	
Greater than 13	129	101 (30.4)	28 (31.5)	
		Demographics		
Age at diagnosis:				0.94
Less than 55	61	49 (14.8)	12 (13.5)	
55—64.9	190	150 (45.2)	40 (44.9)	
65 or Greater	170	133 (40.0)	37 (41.6)	
Race:				0.43
White	382	302 (91.0)	80 (89.9)	
Black	19	13 (3.9)	6 (6.7)	
Other	20	19 (5.1)	3 (3.4)	
Ethnicity:				0.33
Hispanic	17	15 (4.5)	2 (2.3)	
NonHispanic	404	317 (95.5)	87 (97.7)	
		Clinical factors		
Family history:				0.74
Pos	103	84 (25.3)	19 (21.4)	
Neg	300	234 (70.5)	66 (74.24)	
Missing	18	14 (4.2)	4 (4.4)	
BMI (kg/m^2):				<0.015
Less than 25	100	76 (22.9)	24 (27.0)	
25—29.9	215	177 (53.3)	38 (42.7)	
30—34.9	71	59 (17.8)	12 (13.5)	
35 or Greater	35	20 (6.0)	15 (16.8)	
		Ca + biopsy related covariates		
PSA (ng/ml):				0.22
Less than 4	125	105 (31.6)	20 (22.4)	
4—10	270	208 (62.7)	62 (69.7)	
10—20	37	19 (5.7)	7 (7.9)	
PSAD (ng):				<0.01
Less than 0.15	291	241 (72.6)	50 (56.2)	
0.15 or Greater	130	91 (27.4)	39 (43.8)	
DRE:				0.31
Benign	358	284 (88.2)	74 (84.1)	
Suspicious	52	38 (11.8)	14 (15.9)	
NCCN risk:				0.46
Low/very low	395	313 (94.3)	82 (92.1)	
Intermediate	26	19 (5.7)	8 (7.9)	
CAPRA score:*				0.22
0	19	18 (5.4)	1 (1.1)	
1	291	226 (68.1)	65 (73.0)	
2	87	71 (21.4)	16 (18.0)	
3	24	17 (5.1)	7 (7.9)	
TRUS prostate vol (cm^3):				0.06
Less than 30	112	84 (25.3)	28 (31.5)	
30—50	171	130 (39.2)	41 (46.1)	
Greater than 50	138	118 (35.5)	20 (22.4)	
Diagnostic biopsy site:				0.85
Study center	162	127 (38.3)	35 (39.3)	
Off site	259	205 (61.7)	54 (60.7)	

* No score greater than 3.

number of reports have presented good clinical outcomes in such men who remain on surveillance.[21,22] The overall impact of this observation may increase the acceptability of AS for men with lower risk PCa.

A notable additional observation was that both PSAD and BMI were associated with disease reclassification. While these variables have been previously reported as predictors of tumor aggressiveness, we found more specifically that PSAD

greater than 0.15 ng was associated with a twofold increase in the odds of reclassification compared to men with PSAD less than 0.15 ng. This relationship has been noted in series comparing prostate biopsy and radical prostatectomy tumor grade.[23,24]

We found that BMI greater than 35 kg/m^2 was associated with an even greater, threefold increase in the odds of reclassification compared to less than 25 kg/m^2. This has also been previously observed as well as higher stage disease in obese men eligible for AS.[25,26] As such, men with PSAD greater than 0.15 ng or with higher BMI could be considered for biopsy around 6 months after diagnosis (the median interval in the lowest tertile) or enhanced rebiopsy techniques such as saturation biopsy, apical biopsy, transition zone biopsy[27] and multiparametric MRI fusion biopsy.[28] These techniques have emerging and yet incompletely defined roles in determining eligibility for continued surveillance.[29] In the Canary PASS, the utilization of multiparametric MRI fusion biopsy is determined by providers at the PASS sites. PASS has implemented mechanisms to capture these data for analysis in ongoing study.

Importantly, the impact of more aggressive imaging and biopsy interventions has not been found to improve the primary purpose of PCa early detection, which is a reduction in PCa mortality. To our knowledge mortality as an end point for MRI use has not been studied in an AS population. Currently, most men still undergo systematic TRUS biopsy for both initial diagnosis and surveillance biopsy, and MRI is not considered the standard of care or a replacement for systematic biopsy.[3,30] Finally, the converse point is that among men without elevated PSAD and BMI it may be reasonable to defer the first AS biopsy for up to 15 months, which was the median interval in the longest tertile.

Our study is not without limitations. It is observational and under sampled nonwhite men. However, the findings in this study generate hypotheses for further investigation. Nonetheless, the prospective nature of the trial minimizes recall and other biases. The duration of followup was too short to analyze PCa long-term end points (PCa specific morality and overall survival). Similarly, the number of patients undergoing treatment was too low to analyze intermediate end points (adverse pathology, secondary therapy and biochemical recurrence). Due to the PASS protocol recommendations, participants generally undergo the first AS biopsy within the first year of diagnosis so that the conclusions of this analysis cannot be translated to patients who undergo the first AS biopsy after significantly longer periods. Finally, pathology review in PASS relies on genitourinary pathologists at each study site so that some intersite variation is almost certainly operational. However, analogous to intent to treat methodology in randomized trials, some minor variation in pathology reporting may more accurately reflect community practice and could increase generalizability of these results.

CONCLUSIONS

The time between the initial and the first AS biopsy is not associated with PCa reclassification. Overall, about 1 of 5 men will be reclassified at the first AS biopsy. Higher PSAD and BMI are associated with an increased risk of PCa reclassification on the first AS biopsy. In such patients, an earlier (less than 8 months) and/or enhanced biopsy may be appropriate. These data should be helpful in both counseling and treating men considering AS for initial management of lower risk PCa.

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