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

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Abstract

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

Materials/Methods—Of 1,085 participants in PASS, 421 had <34% cores involved with cancer, Gleason sum ≤6, and thereafter underwent on-study AS biopsy. Reclassification was defined as increase in Gleason sum and/or ≥34% of cores with PCa. First AS biopsy reclassification rates were categorized as <8, 8–13 and >13 months post-diagnosis. Multivariable logistic regression determined association between reclassification and first biopsy timing.

Results—Of 421 men, 89 (21.1%) experienced reclassification at first AS biopsy. Median time from PCa diagnosis to first AS biopsy was 11 months (IQR 7.8–13.8). Reclassification rates at <8,

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8–13 and >13 months were 24%, 19%, and 22%, (p=0.65). On multivariable analysis, compared to men biopsied at <8 months the odds ratios (OR) of reclassification at 8–13 and >13 months were 0.88 (95%CI 0.5,1.6) and 0.95 (95% CI 0.5,1.9), respectively. PSA density ≥0.15 (reference <0.15, OR 1.9 [95%CI 1.1, 4.1]) and body mass index (BMI) ≥35 (reference <25 kg/m^2, OR 2.4 [95%CI 1.1,5.7]) were associated with increased odds of reclassification.

Conclusions—Timing of first AS biopsy was not associated with increased adverse reclassification but PSA density and BMI were. In low-risk patients on AS, it may be reasonable to perform first AS biopsy at a later time, reducing overall cost and morbidity of AS.

Keywords

localized prostate cancer; active surveillance; low risk prostate cancer; progression; reclassification

Introduction

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

Management of low-risk PCa patients with Active Surveillance (AS) may reduce the risk of over-treatment by delaying therapy and treating only those developing clinically-significant malignancy. Patients on AS undergo monitoring with PSA measurements, digital rectal exams (DRE), and prostate biopsies. AS suffers from limited data supporting the superiority of any specific follow-up schedule.[6]

The decision to abandon AS and initiate therapy is usually based on factors including changes in PSA, DRE, 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 transrectal ultrasound-guided (TRUS) biopsy can miss tumors of greater biologic 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 first AS biopsy 6–12 months post-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 on 5 year outcomes in the Canary Prostate Cancer Active Surveillance (PASS) study.[12] The current study was designed to specifically address optimal timing of first AS biopsy. We sought to define rates of adverse reclassification (hence reclassification) on first AS biopsy, stratified by timing of first AS biopsy. We hypothesized

that among men having first AS biopsy in the recommended timeframe 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 (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 (FHCRC; Coordinating Center), and 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.[12] For this study, data were frozen March 25, 2014 when 1,085 men were enrolled.

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

The PASS protocol recommends performing the first AS biopsy 6–12 months post-diagnosis. Although there is heterogeneity, resulting in first AS biopsy >12 months post-diagnosis for some. Biopsies were all TRUS-guided with ≥10 cores. Magnetic resonance imaging (MRI) fusion technology was not available as 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 cores. First AS biopsy timing was categorized based approximately on tertiles, reflecting practice within PASS: <8 months, 8–13 months and >13 months post-diagnostic biopsy. Given the lack of consensus on first surveillance biopsy timing, these three intervals are potentially meaningful cut-points for early, intermediate and deferred first AS biopsy. Multivariate logistic regression determined association between reclassification, first AS biopsy timing, and other covariates. For this analysis, biopsy specimens were evaluated for Gleason score by genitourinary pathologists at PASS sites using the 2005 World Health Organization/International Society of Urologic Pathologists modified Gleason system.[14] Central pathology review was not performed.

De-identified demographic, clinical, and pathologic data are centrally maintained at FHCRC and managed by the National Cancer Institute's 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 first AS biopsy. The primary outcome was rate of reclassification on first AS biopsy, defined as any Gleason pattern ≥4 or increase to ≥34% cores with cancer on first AS biopsy. Descriptive data are also provided on sub-types of

reclassification given possible gradations in prognosis (i.e., primary Gleason pattern compared to secondary Gleason pattern reclassification, 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, ethnicity), co-morbidities (family history, body mass index [BMI kg/m^2]) and oncologic/pathologic features (diagnostic PSA, diagnostic PSA density [PSAD], DRE characteristics, NCCN risk stratum[3], Cancer of the Prostate Risk Assessment (CAPRA) score[16], clinical stage classification, diagnostic TRUS volume, and location of diagnostic biopsy [study site/referred-in]).

Statistical Analysis

Continuous variables were categorized as shown in table 1. Multivariable logistic regression was used to model factors associated with adverse reclassification on first AS biopsy. Both unadjusted and multivariable models were applied. All *a priori* covariates were included in the unadjusted model. Then the multivarariable model was backward selected in stepwise fashion with a pre-set significance level for inclusion of $p<0.2$ in order to minimize overfitting the model (included variables shown in Table 4). The Hosmer-Lemshow goodness of fit test assessed model specification[17] and the c-statistic (area under the curve) was calculated to determine predictive accuracy of the model [18]. Several sensitivity analyses assessed selection of cut-points for continuous variables. Both PSA at diagnosis and 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 follow 30 months (range 3–71) and median time to first AS biopsy 11 months (range 4–28 months). For the tertile subgroups, median time to first AS biopsy was 6.3 months (IQR 5.8–7.7), 11.5 months (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 first AS biopsy. Overall, 89 men (21.1%) were reclassified at first AS biopsy. There was no difference in reclassification rate whether first AS biopsy was at <8 months (23.5%), 8–13 months (19.2%), or >13 months (21.7%) (chi-squared p=0.65). Additionally, 144 men (34%) had no cancer identified on first AS biopsy. Most of the participants were diagnosed after age 55, racially identified as white, had negative family history and BMI<30 kg/m^2. Approximately 6% of men were NCCN intermediate risk (26/421) or had a CAPRA score >2. The few men who were intermediate risk were so classified based on PSA (>10 ng/ml). On baseline chi-squared comparison, the three biopsy timing groups were well balanced except that men diagnosed at a community center and

then referred to PASS were more likely to have first AS biopsy in the <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 2). Grade reclassification affected 77/89 (86.5%) of reclassified men. The most common pattern of reclassification in 43/89 (48.3%) of patients was to primary Gleason pattern 3 with secondary pattern ≥4 and no increase to ≥34% core involvement. Concurrent volume and grade reclassification affected 7/89 men (7.8%, i.e. both primary Gleason 4/volume increase to ≥34% core involvement). Among the men reclassified for increase in secondary Gleason pattern, two had secondary pattern 5, but none had primary pattern 5. Importantly, we verified that among the 7/89 men with primary Gleason 4 *and* volume increase, there was no difference in rates of reclassification at the <8, 8–13 or >13-month biopsy intervals (chi-squared p=0.94). Similarly, among the 19/89 men reclassified with primary pattern 4, there was no difference based on tertile of timing (p=0.60).

The cohort is stratified by reclassification status in Table 3. BMI and PSAD were associated with reclassification on baseline chi-squared analysis. In unadjusted logistic regression (Table 4), BMI>35 kg/m^2 (reference<25kg/m^2), and PSAD>0.15 (reference<0.15) were associated with reclassification. In a multivariable model adjusting for all covariates, BMI>35 kg/m^2 was associated with a greater than 3-fold increase in the odds of reclassification and PSAD>0.15 was associated with a 2-fold increase in the odds of reclassification (compared to their respective referent groups, Table 4). The results were no different when repeating these models with time 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 first AS biopsy (data not shown). The Hosmer-Lemshow p-value for the final model was 0.65, leading us to reject the hypothesis that the model was overfit and the AUC for the model was 0.67.

Discussion

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

Our finding of a rate of 21% reclassification at first AS biopsy is consistent with other series, with rates ranging from 15–42%.[19, 20] Additionally, in low-risk AS patients, median time to reclassification is reported as around 2 years [21], resulting in a clinical dilemma between detection of occult aggressive disease and making AS more cost-effective/tolerable. The rate of reclassification was not significantly affected by the time to first AS biopsy, within the range of times-to-biopsy observed in this study supporting the notion that the reclassification

of the vast majority of men was due to sampling error in the diagnostic biopsy rather than biologic disease progression.

During initial counseling regarding treatment of low-risk, localized PCa, men should be informed that approximately one in five men who initially opt for surveillance will have more aggressive disease on 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 timing of 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 felt 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 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, PSAD>0.15 was associated with 2-fold increase in the odds of reclassification compared to men with PSAD<0.15. This relationship has been noted in series comparing prostate biopsy and radical prostatectomy tumor grade.[23,24] We found BMI>35 kg/m^2 was associated with an even greater, 3-fold increase in the odds of reclassification (compared to <25kg/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 > 0.15 or with higher BMI, could be considered for biopsy around 6 months after diagnosis (the median interval in the lowest tertile) or enhanced re-biopsy techniques such as saturation biopsy, apical biopsy, transition zone biopsy[27] and multiparametric magnetic resonance imaging (mpMRI) fusion biopsy[28]. These techniques have emerging, yet incompletely defined, roles in determining eligibility for continued surveillance[29]. In the Canary PASS study, utilization of mpMRI 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 have not been found to improve the primary purpose of PCa early detection: a reduction in PCa mortality, though mortality as an endpoint for MRI utilization has not been studied to our knowledge in an AS population. Currently, most men still undergo systematic TRUS biopsy for both initial diagnosis as well as surveillance biopsy, and MRI is not considered standard of care, nor 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 first AS biopsy up to 15 months (median interval in the longest tertile).

Our study is not without limitations; it is observational and under sampled non-whites. However, the findings in this study do generate hypotheses for further investigation. Nonetheless, the prospective nature of the trial minimizes recall and other biases. The duration of follow up is too short to analyze PCa long term endpoints (PCSM, overall survival). Similarly, the number of patients undergoing treatment is too low to analyze intermediate endpoints (adverse pathology, secondary therapy, biochemical recurrence). Due

to PASS protocol recommendations, participants generally undergo first AS biopsy within the first year of diagnosis, and the conclusions of this analysis cannot be translated to patients who underwent their first AS biopsy after significantly longer periods of time. Finally, pathology review in PASS relies on genitourinary pathologists at each study site; some inter-site 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 initial and first AS biopsy is not associated with PCa reclassification. Overall, about 1 in 5 men will be reclassified at first AS biopsy. Higher PSAD and BMI are associated with increased risk of PCa reclassification on first AS biopsy; in such patients, an earlier (<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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Legend

AS	active surveillance
BMI	body mass index
DRE	digital rectal exam
FHRC	Fred Hutchinson Cancer Research Center
mpMRI	multiparametric MRI
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

References

1. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA. 2005; 293:2095. [PubMed: 15870412]
2. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol. 2010; 28:1117. [PubMed: 20124165]
3. Mohler, JL., Armstrong, AJ., Cohen, M., D'Amico, AV., Eastham, JA., Enke, CA., Farrington, TA., Higano, CS., et al. National Comprehensive Cancer Network Guidelines in Oncology: Prostate Cancer. Vol. 1.2015. Fort Washington, PA: NCCN Foundation; 2015.
4. Miller DC, Gruber SB, Hollenbeck BK, et al. Incidence of initial local therapy among men with lower-risk prostate cancer in the United States. J Natl Cancer Inst. 2006; 98:1134. [PubMed: 16912266]
5. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized Prostate Cancer, 1990–2013. JAMA. 2015; 314:80. [PubMed: 26151271]
6. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol. 2012; 62:976. [PubMed: 22698574]
7. Penson DF. Factors influencing patients' acceptance and adherence to active surveillance. J Natl Cancer Inst Monogr. 2012; 2012:207. [PubMed: 23271775]
8. Motamedinia P, RiChard JL, McKiernan JM, et al. Role of immediate confirmatory prostate biopsy to ensure accurate eligibility for active surveillance. Urology. 2012; 80:1070. [PubMed: 23107398]
9. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. Eur Urol. 2013; 63:597. [PubMed: 23159452]
10. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol. 2011; 29:2185. [PubMed: 21464416]
11. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. J Clin Oncol. 2010; 28:126. [PubMed: 19917860]
12. Newcomb LF, Thompson IM Jr, Boyer HD, et al. Outcomes of Active Surveillance for Clinically Localized Prostate Cancer in the Prospective, Multi-Institutional Canary PASS Cohort. J Urol. 2016; 195:313. [PubMed: 26327354]
13. Newcomb LF, Brooks JD, Carroll PR, et al. Canary Prostate Active Surveillance Study: design of a multi-institutional active surveillance cohort and biorepository. Urology. 2010; 75:407. [PubMed: 19758683]
14. Epstein JI, Allsbrook WC Jr, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol. 2005; 29:1228. [PubMed: 16096414]
15. Adamy A, Yee DS, Matsushita K, et al. Role of prostate specific antigen and immediate confirmatory biopsy in predicting progression during active surveillance for low risk prostate cancer. J Urol. 2011; 185:477. [PubMed: 21167529]
16. Cooperberg MR, Pasta DJ, Elkin EP, et al. The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. J Urol. 2005; 173:1938. [PubMed: 15879786]
17. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol. 1982; 115:92. [PubMed: 7055134]
18. Austin PC, Steyerberg EW. Interpreting the concordance statistic of a logistic regression model: relation to the variance and odds ratio of a continuous explanatory variable. BMC Med Res Methodol. 2012; 12:82. [PubMed: 22716998]
19. Porten SP, Whitson JM, Cowan JE, et al. Changes in prostate cancer grade on serial biopsy in men undergoing active surveillance. J Clin Oncol. 2011; 29:2795. [PubMed: 21632511]
20. Shapiro RH, Johnstone PA. Risk of Gleason grade inaccuracies in prostate cancer patients eligible for active surveillance. Urology. 2012; 80:661. [PubMed: 22925240]

21. Hussein AA, Welty CJ, Ameli N, et al. Untreated Gleason Grade Progression on Serial Biopsies during Prostate Cancer Active Surveillance: Clinical Course and Pathological Outcomes. J Urol. 2015; 194:85. [PubMed: 25623742]
22. Cooperberg MR, Cowan JE, Hilton JF, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. J Clin Oncol. 2011; 29:228. [PubMed: 21115873]
23. Corcoran NM, Casey RG, Hong MK, et al. The ability of prostate-specific antigen (PSA) density to predict an upgrade in Gleason score between initial prostate biopsy and prostatectomy diminishes with increasing tumour grade due to reduced PSA secretion per unit tumour volume. BJU Int. 2012; 110:36. [PubMed: 22085203]
24. San Francisco IF, Werner L, Regan MM, et al. Risk stratification and validation of prostate specific antigen density as independent predictor of progression in men with low risk prostate cancer during active surveillance. J Urol. 2011; 185:471. [PubMed: 21167525]
25. Bhindi B, Kulkarni GS, Finelli A, et al. Obesity Is Associated with Risk of Progression for Low-risk Prostate Cancers Managed Expectantly. Eur Urol. 2014; 66:841. [PubMed: 24954793]
26. Ploussard G, de la Taille A, Bayoud Y, et al. The risk of upstaged disease increases with body mass index in low-risk prostate cancer patients eligible for active surveillance. Eur Urol. 2012; 61:356. [PubMed: 21803484]
27. Wong LM, Toi A, Van der Kwast T, et al. Regular transition zone biopsy during active surveillance for prostate cancer may improve detection of pathological progression. J Urol. 2014; 192:1088. [PubMed: 24742593]
28. Patel AR, Jones JS. Optimal biopsy strategies for the diagnosis and staging of prostate cancer. Curr Opin Urol. 2009; 19:232. [PubMed: 19365892]
29. Guo R, Cai L, Fan Y, et al. Magnetic resonance imaging on disease reclassification among active surveillance candidates with low-risk prostate cancer: a diagnostic meta-analysis. Prostate Cancer Prostatic Dis. 2015; 18:221. [PubMed: 25986915]
30. Chen RC, Rumble RB, Loblaw DA, et al. Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol. 2016; 34:2182. [PubMed: 26884580]

Table 1

Baseline characteristics of the Canary Prostate Active Surveillance Study sub-cohort stratified by interval (tertiles) from diagnostic biopsy to first active surveillance (AS) biopsy

	Subgroup (N)	**<8 months 119 (28.3%)**	**8–13 months 173 (41.1%)**	**>13 months 129 (30.6%)**	**P-value[1]**
Outcome					
Reclassified on[2] First AS biopsy	Gleason (77)	25 (21.0)	25 (14.5)	27 (20.9)	0.29
	Volume (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	<55 (61)	15 (12.6)	26 (15.0)	20 (15.5)	0.43
	55–64.9 (190)	53 (44.5)	86 (49.7)	51 (39.5)	
	≥65 (170)	51 (42.9)	61 (35.3)	58 (45.0)	
Race	White (382)	106 (89.1)	157 (90.8)	119 (92.3)	0.49
	Black (19)	8 (6.7)	5 (2.9)	6 (4.6)	
	Other (20)	5 (4.2)	11 (6.3)	4 (3.1)	
Ethnicity	Hispanic (17)	2 (1.7)	6 (3.5)	9 (7.0)	0.09
	Non-Hispanic (404)	117 (98.3)	167 (96.5)	120 (93.0)	
Clinical factors					
Family history	Positive (103)	35 (29.4)	43 (24.8)	25 (19.4)	0.42
	Negative (300)	79 (66.4)	124 (71.7)	97 (75.2)	
	Missing (18)	5 (4.2)	6 (3.5)	7 (5.4)	
Body Mass Index (kg/m^2)	<25 (100)	25 (21.0)	49 (28.3)	26 (20.2)	0.18
	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 (35)	8 (6.7)	11 (6.4)	16 (12.4)	
Cancer and biopsy-related covariates					
PSA (ng/ml)	<4 (125)	29 (24.4)	58 (33.5)	38 (29.4)	0.26
	4–10 (270)	79 (66.4)	105 (60.7)	86 (66.7)	
	10–20 (37)	11 (9.2)	10 (5.8)	5 (3.9)	

	Subgroup (N)	<8 months 119 (28.3%)	8–13 months 173 (41.1%)	>13 months 129 (30.6%)	P-value[1]
PSA Density (ng)	<0.15 (291)	77 (64.7)	119 (68.8)	95 (73.6)	0.31
	≥0.15 (130)	42 (35.3)	54 (31.2)	34 (26.3)	
Digital Rectal Exam[4]	Benign (358)	106 (90.6)	139 (83.7)3	113 (89.0)	0.18
	Suspicious (52)	11 (9.4)	27 (16.3)	14 (11.0)	
NCCN	Low/Very Low (395)	108 (90.8)	163 (94.2)	124 (96.1)	0.20
	Intermediate (26)	11 (9.2)	10 (5.8)	5 (3.9)	
Cancer of the Prostate Risk Assessment Score (CAPRA)[3]	0 (19)	4 (3.4)	7 (4.0)	8 (6.2)	0.61
	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)	
Prostate Volume by TRUS (cm^3)	<30 (112)	23 (19.3)	50 (28.9)	39 (30.2)	0.16
	30–50 (171)	56 (47.1)	71 (41.0)	44 (34.1)	
	>50 (138)	40 (33.6)	52 (30.1)	46 (35.7)	
Location diagnostic biopsy	Study Center (162)	31 (26.1)	82 (47.4)	49 (38.0)	<0.01
	Off site (259)	88 (73.9)	91 (53.6)	80 (62.0)	

[1] Chi-squared tests.

[2] N (% of cohort with first AS biopsy in that time period)

[3] No CAPRA >3 in cohort.

[4] Missing data on 10 men.

Table 2

Reasons for adverse prostate cancer reclassification in the 89 men in the Canary Prostate Active Surveillance Study reclassified at the time of first active surveillance biopsy

	No Grade Reclassification (Gleason Pattern 3+3) N(%[1])	Grade Reclassification (Gleason pattern 3+4) N(%[1])	Grade Reclassification (Gleason Pattern 4+3) N(%[1])
No volume reclassification (<34% cores involved in cancer)	N/A	43 (48.3%)	12 (13.5%)
Volume Reclassification (≥34% cores involved in cancer)	12 (13.5%)	15 (16.9%)	7 (7.8%)

[1]Percent of the 89 reclassified men.

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Table 3

Canary Prostate Cancer Active Surveillance Study cohort reclassification status at first AS biopsy stratified by clinically relevant variables

	Substratum (N)	**Not Reclassified 332 (78.9%)**	**Reclassified N 89 (21.1%)**	**P-value[1]**
Outcomes				
First AS biopsy timing	< 8 months (119)	91 (27.4)	28 (31.5)	0.65
	8–13 months (173)	140 (42.2)	33 (37.1)	
	>13 months (129)	101 (30.4)	28 (31.5)	
Demographics				
Age at diagnosis	<55 (61)	49 (14.8)	12 (13.5)	0.94
	55–64.9 (190)	150 (45.2)	40 (44.9)	
	≥65 (170)	133 (40.0)	37 (41.6)	
Race	White (382)	302 (91.0)	80 (89.9)	0.43
	Black (19)	13 (3.9)	6 (6.7)	
	Other (20)	19 (5.1)	3 (3.4)	
Ethnicity	Hispanic (17)	15 (4.5)	2 (2.3)	0.33
	Non-Hispanic (404)	317 (95.5)	87 (97.7)	
Clinical factors				
Family history	Positive (103)	84 (25.3)	19 (21.4)	0.74
	Negative (300)	234 (70.5)	66 (7424)	
	Missing (18)	14 (4.2)	4 (4.4)	
Body Mass Index (kg/m^2)	<25 (100)	76 (22.9)	24 (27.0)	<0.015
	25–29.9 (215)	177 (53.3)	38 (42.7)	
	30–34.9 (71)	59 (17.8)	12 (13.5)	
	≥35 (35)	20 (6.0)	15 (16.8)	
Cancer and biopsy-related covariates				
PSA (ng/ml)	<4 (125)	105 (31.6)	20 (22.4)	0.22
	4–10 (270)	208 (62.7)	62 (69.7)	
	10–20 (37)	19 (5.7)	7 (7.9)	
PSA Density (ng)	<0.15 (291)	241 (72.6)	50 (56.2)	<0.01

	Substratum (N)	Not Reclassified 332 (78.9%)	Reclassified N 89 (21.1%)	P-value[1]
	≥0.15 (130)	91 (27.4)	39 (43.8)	
Digital Rectal Exam	Benign (358)	284 (88.2)	74 (84.1)	0.31
	Suspicious (52)	38 (11.8)	14 (15.9)	
NCCN	Low/Very Low (395)	313 (94.3)	82 (92.1)	0.46
	Intermediate (26)	19 (5.7)	8 (7.9)	
Cancer of the Prostate Risk Assessment Score (CAPRA) [2]	0 (19)	18 (5.4)	1 (1.1)	0.22
	1 (291)	226 (68.1)	65 (73.0)	
	2 (87)	71 (21.4)	16 (18.0)	
	3 (24)	17 (5.1)	7 (7.9)	
Prostate Volume by TRUS (cm^3)	<30 (112)	84 (25.3)	28 (31.5)	0.06
	30–50 (171)	130 (39.2)	41 (46.1)	
	>50 (138)	118 (35.5)	20 (22.4)	
Location diagnostic biopsy	Study Center (162)	127 (38.3)	35 (39.3)	0.85
	Off site (259)	205 (61.7)	54 (60.7)	

[1] Chi-squared tests.

[2] No CAPRA >3 in cohort.

Table 4

Logistic regression models of association between reclassification on first active surveillance biopsy and clinical variables

		Unadjusted OR (95% CI)	Multivariable OR (95% CI)
First AS biopsy timing	<8 months	Ref	Ref
	8–13 months	0.80 (0.45, 1.40)	0.78 (0.43, 1.41)
	>13 months	0.91 (0.53, 1.63)	0.89 (0.47, 1.67)
Age at diagnosis	<55	Ref	Not included
	55–64.9	1.04 (0.53, 2.28)	
	65+	1.17 (0.56, 2.41)	
Race	White	Ref	Not included
	Black	1.70 (0.79, 5.26)	
	Other	0.67 (0.19, 2.33)	
Ethnicity	Hispanic	0.48 (0.11, 2.14)	Not included
	Non-Hispanic	Ref	
Family history	Positive	0.79 (0.44, 1.39)	Not included
	Negative	Ref	
	Missing	1.00 (0.32, 3.13)	
Body Mass Index (kg/m^2)	<25	Ref	Ref
	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+	**3.00 (1.50, 6.21)**	**2.67 (1.14, 6.21)**
PSA (ng/ml)	<4	Ref	Ref
	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)**
PSA Density (ng)	<0.15	Ref	Ref
	0.15+	**2.05 (1.31, 3.48)**	**1.96 (1.12, 4.13)**
Digital Rectal Exam	Benign/Enlarged	Ref	Not included
	Suspicious	1.39 (0.71, 2.70)	
NCCN	Low/Very Low	Ref	Not included
	Intermediate	1.41 (0.57, 3.46)	
Cancer of the Prostate Risk Assessment Score (CAPRA)	0	Ref	Not included
	1	5.18 (0.68. 39.5)	
	2	4.06 (0.50, 32.1)	
	3	8.47 (0.96, 75.1)	
Prostate Volume by TRUS (cm^3)	<30	Ref	Ref
	30–50	0.95 (0.54, 1.65)	1.11 (0.57, 2.15)
	>50	0.53 (0.28, 1.09)	0.57 (0.25, 1.28)
Site of diagnostic biopsy	Study Center	1.08 (0.67, 1.73)	Not included
	Off site	Ref	

Statistically significant covariates are **bolded**. Multivariable model was backward selected as described in the text.