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# Role of Surveillance Biopsy with No Cancer as a Prognostic Marker for Reclassification: Results from the Canary Prostate Active Surveillance Study

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**Abstract**

***Background:*** Many patients who are on active surveillance (AS) for prostate cancer will have surveillance prostate needle biopsies (PNBs) without any cancer evident.
***Objective:*** To define the association between negative surveillance PNBs and risk of reclassification on AS.
***Design, setting, and participants:*** All men were enrolled in the Canary Prostate Active Surveillance Study (PASS) between 2008 and 2016. Men were included if they had Gleason $\leq 3+4$ prostate cancer and $<34\%$ core involvement ratio at diagnosis. Men were prescribed surveillance PNBs at 12 and 24 mo after diagnosis and then every 24 mo.
***Outcome measurements and statistical analysis:*** Reclassification was defined as an increase in Gleason grade and/or an increase in the ratio of biopsy cores to cancer to $\geq 34\%$. PNB outcomes were defined as follows: (1) no cancer on biopsy, (2) cancer without reclassification, or (3) reclassification. Kaplan–Meier and Cox proportional hazard models were performed to assess the risk of reclassification.
***Results and limitations:*** A total of 657 men met inclusion criteria. On first surveillance PNB, 214 (32%) had no cancer, 282 (43%) had cancer but no reclassification, and 161 (25%) reclassified. Among those who did not reclassify, 313 had a second PNB. On second PNB, 120 (38%) had no cancer, 139 (44%) had cancer but no reclassification, and 54 (17%) reclassified. In a multivariable analysis, significant predictors of decreased future reclassification after the first PNB were no cancer on PNB (hazard ratio [HR] = 0.50, $p = 0.008$), lower serum prostate-specific antigen, larger prostate size, and lower body mass index. A finding of no cancer on the second PNB was also associated with significantly decreased future reclassification in a multivariable analysis (HR = 0.15, $p = 0.003$), regardless of the first PNB result. The major limitation of this study is a relatively small number of patients with long-term follow-up.
***Conclusions:*** Men who have a surveillance PNB with no evidence of cancer are significantly less likely to reclassify on AS in the PASS cohort. These findings have implications for tailoring AS protocols.
***Patient summary:*** Men on active surveillance for prostate cancer who have a biopsy showing no cancer are at a decreased risk of having worse disease in the future. This may have an impact on how frequently biopsies are required to be performed in the future.


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## 1. Introduction

Active surveillance (AS) for prostate cancer is an increasingly popular management strategy for Gleason 3 + 3 and low-volume 3 + 4 prostate cancer [1]. Patients are generally assessed by periodic serum prostate-specific antigen (PSA) testing, digital rectal examination, and prostate biopsy. Despite increasing use, an optimal AS protocol that defines precise timing of these assessments has not yet been established or defined by practice guidelines. In published series, biopsies are performed as frequently as annually [2] to every 3–4 yr [3]. Furthermore, within a given protocol, there has been no formal strategy for tailoring biopsy frequency based on a patient's individualized risk.

Prostate biopsies yield a wealth of information about an individual's cancer, but many men find them to be unpleasant, the biopsies are costly [4], and there is an approximately 5% risk of infection following biopsy [5]. Furthermore, published AS series report that although the majority of surveillance biopsies find no change in the Gleason grade, 21–50% [6] of surveillance biopsies have no cancer found on the biopsy specimens, suggesting a low cancer volume. Given these considerations, it is a common clinical scenario for an AS patient who has one or more surveillance biopsies with the finding of no cancer to question the need for further biopsy.

In this context, we examined the predictive value of no cancer on surveillance biopsy for future pathological reclassification after a diagnosis of very-low– and low-risk prostate cancer in the large, multicenter Canary Prostate Active Surveillance Study (PASS). We assessed the significance of biopsy results in the first and second biopsies after the initial diagnosis and performed modeling to take into account variables that contribute to risk of reclassification.

## 2. Patients and methods

### 2.1. Patient population

PASS is a multi-institutional prostate cancer AS cohort study in North America [7]. All patients were enrolled in PASS and approved by institutional review boards at all participating sites (clinicaltrials.gov NCT000756665). Under the PASS protocol, PSA is measured every 3 mo, clinic visits occur every 6 mo, and ultrasound-guided biopsies are performed first between 6 and 12 mo after diagnosis, second at 24 mo after diagnosis, and then every 2 yr. In addition, the PASS protocol allows for off-protocol, "for-cause" biopsies. Eighty percent of biopsies were per protocol (on time), with 20% occurring either earlier or later than the protocol schedule. At least 10-core templates were required, with the median (interquartile range [IQR]) number of total biopsy cores collected being 12 (12, 14). Other tests, including magnetic resonance imaging (MRI), may be performed at the clinicians' discretion, but as the study started enrollment in 2008, the majority of men have not undergone these procedures. Patients were included in the current analysis if they were enrolled as of February 2016, had Gleason $\leq$3 + 4 prostate cancer, had <34% ratio of biopsy cores containing cancer to total biopsy cores (core ratio) at diagnosis, and had their first surveillance biopsy after the initial diagnosis of prostate cancer (aka, confirmatory biopsy) within 2 yr of diagnosis and while enrolled in PASS.

### 2.2. Outcomes and statistical methods

The primary outcome was time to reclassification from either the first or the second surveillance biopsy. Reclassification was defined as an increase in primary or secondary Gleason grade at biopsy and/or an increase in the core ratio to $\geq$34%. All pathology outcomes were determined by uropathologists at each site. Sensitivity analyses were also performed for participants diagnosed with Gleason 3 + 3 only or for grade-only reclassification. Patients without reclassification were censored on the date of last study contact, treatment, or 2 yr after their last biopsy, whichever came first.

Patients were stratified by the outcome of their first or second surveillance biopsy as follows: (1) no evidence of cancer on biopsy, (2) evidence of cancer on biopsy without reclassification, or (3) reclassification. Kaplan–Meier curves were plotted to examine how reclassification-free probability varied with surveillance biopsy outcome over the follow-up period. Log-rank tests were used to compare differences in reclassification-free probabilities.

Associations between previous surveillance biopsy result (no cancer vs cancer without reclassification) and time to future reclassification were modeled using Cox proportional hazard models. In order to assess whether the first surveillance biopsy result was associated with future reclassification, we considered a time since first surveillance biopsy model, where the association of interest was the result of the first surveillance biopsy. In order to assess whether the aggregate effect of the first and second surveillance biopsy results was associated with future reclassification, we considered a time since second surveillance biopsy model, where the two associations of interest were the results of the first and second surveillance biopsies, respectively. Owing to our hypotheses of interest, previous surveillance biopsy result(s) remained in the two models regardless of statistical significance. In addition, the following covariates were considered: natural log-transformed PSA closest and prior to surveillance biopsy, maximum core ratio from either diagnostic biopsy or surveillance biopsy, natural log-transformed diagnostic PSA, body mass index (BMI), natural log-transformed prostate volume, age at diagnosis, clinical T stage (T1 vs T2), diagnostic Gleason (3 + 4 or 3 + 3), and race (Caucasian vs others). Study site was accounted for by stratifying the baseline hazard. In order to account for potential collinearity among the variables, insignificant covariates were backward eliminated based on a $p$ value cutoff of 0.05.

To address whether our results were biased by a negative biopsy influencing the decision to undergo or delay a biopsy, several steps were taken. The timing of each biopsy was defined as "on time," "early," or "late" based on the PASS protocol. Multinomial regression analyses were used to determine if biopsy timing was associated with prior biopsy result. A sensitivity analysis was performed on a subset of participants with all biopsies compliant to the protocol. Further details are in the Supplementary material. Analyses were performed with SAS version 9.4 and R version 3.3.0.

## 3. Results

Six hundred fifty-seven men were included in this analysis. Overall median follow-up from diagnosis for participants without a reclassification event was 2.9 yr (IQR 1.8–4.7). All participants received a first surveillance biopsy, which occurred at a median of 1.0 yr after diagnosis (IQR 0.7–1.2 yr). The outcomes of the first surveillance biopsy were as follows: 214 (32%) with no cancer on this biopsy, 282 (43%) with cancer on biopsy but no reclassification, and 161 (25%) with reclassification (Fig. 1). Of the 496 men who did not reclassify, 313 had a second biopsy at a median of 2.3 yr

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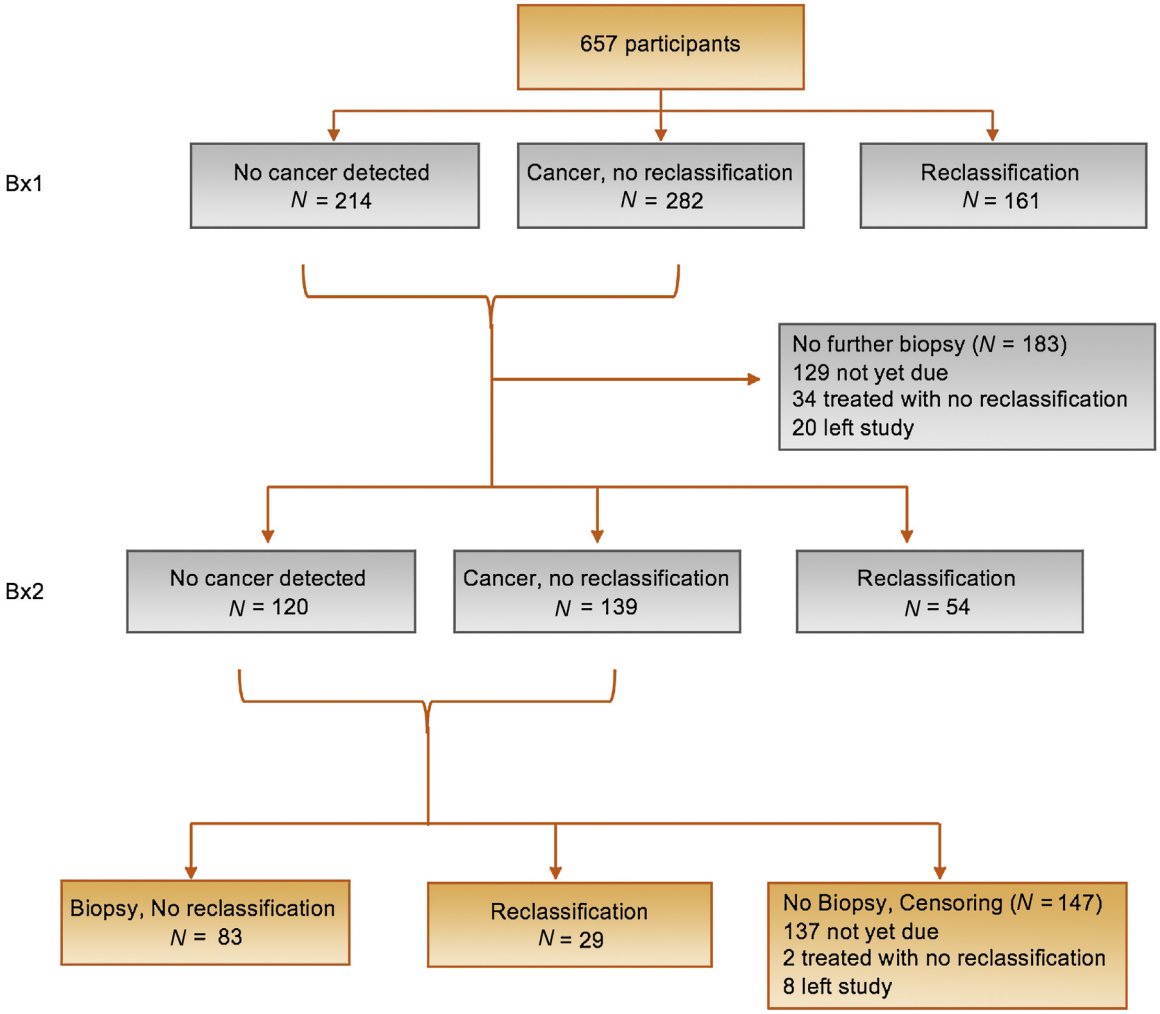


**Fig. 1 – Consort diagram of patients receiving surveillance biopsy and biopsy outcomes. Bx1 = first surveillance biopsy; Bx2 = second surveillance biopsy.**

from diagnosis (IQR 2.0–3.0 yr). Among these 313 men, 120 (38%) had no cancer on this biopsy, 139 (45%) had some cancer but no reclassification, and 54 (17%) had a reclassification event at second biopsy (Fig. 1).

The mean age of the cohort was 63 yr, median PSA was 4.9 ng/ml, median prostate volume was 42 cc, 94% were diagnosed with Gleason 3 + 3, and the median core ratio was 8% (which corresponds to 1/12 biopsy cores with cancer; Table 1). When stratified by the outcome of the first surveillance biopsy, the groups were similar with respect to racial makeup, age, clinical stage, family history of prostate cancer, and BMI. There were statistically significant differences across groups for prostate volume, serum PSA level, PSA density, diagnostic Gleason grade, and diagnostic core ratio positive for prostate cancer (Table 1). The results for patients who underwent a second surveillance biopsy are similar and are given in Supplementary Table 1.

Kaplan–Meier analysis of reclassification stratified by outcome of the first surveillance biopsy is shown in Figure 2. There was a statistically significant difference in time to reclassification in men whose first biopsy had no evidence of cancer versus men having evidence of cancer without reclassification ($p < 0.001$). Similarly, there was a statistically significant difference in time to reclassification based on the outcome of the second biopsy ($p < 0.001$), as shown in Figure 3. When patients who had two surveillance biopsies without reclassification were stratified by outcome of both first and second surveillance biopsies, the reclassification-free probability was similar for patients whose second surveillance biopsy showed no cancer, regardless of the result of the first biopsy (Supplementary Fig. 1).

A first surveillance prostate biopsy negative for any cancer versus positive for cancer without reclassification was associated with less risk of reclassification in future biopsies (hazard ratio [HR] = 0.44, $p < 0.001$). After adjusting for serum PSA, prostate volume, and BMI, no cancer on initial surveillance biopsy was still significantly protective against reclassification (HR 0.50, $p = 0.008$; Table 2). Finding no cancer in the second surveillance biopsy was also significantly protective against reclassification in both unadjusted (HR 0.12, $p < 0.001$) and adjusted (HR 0.18, $p = 0.01$) analyses (Table 3).

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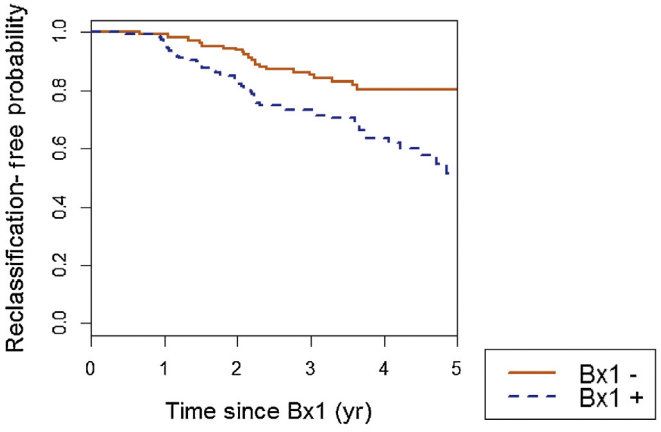
**Table 1 – Patient characteristics based on results of first surveillance biopsy**

| | No cancer 1st surveillance biopsy | Cancer without reclassification 1st surveillance biopsy | Reclassification on 1st surveillance biopsy | *p* value [a] |
|---|---|---|---|---|
| **N** | 214 | 282 | 161 | |
| Race, *n* (%) | | | | 0.12 |
| Caucasian American | 187 (87) | 258 (91) | 143 (89) | |
| African American | 16 (7) | 9 (3) | 13 (8) | |
| Other | 11 (5) | 15 (5) | 5 (3) | |
| Prostate volume (cc), median (IQR) | 46 (34–64) | 43 (32–56) | 36 (27–48) | <0.001 |
| Age (yr), mean (SD) | 62 (7) | 63 (7) | 63 (7) | 0.22 |
| PSA (ng/ml), median (IQR) | 5.1 (3.7–6.6) | 4.7 (3.7–6.1) | 5.3 (4.4–6.6) | 0.02 |
| PSA density, median (IQR) | 0.10 (0.07–0.14) | 0.11 (0.08–0.15) | 0.15 (0.11–0.21) | <0.001 |
| Clinical stage, *n* (%) | | | | 0.37 |
| T1a-T1c | 197 (92) | 249 (88) | 146 (91) | |
| T2a-T2c | 17 (8) | 33 (12) | 15 (9) | |
| Diagnostic Gleason score, *n* (%) | | | | 0.03 |
| 3 + 3 | 208 (97) | 259 (92) | 148 (92) | |
| 3 + 4 | 6 (3) | 23 (8) | 13 (8) | |
| Diagnostic core ratio, median (IQR) [b] | 8 (8–14) | 13 (8–17) | 17 (8–18) | <0.001 |
| Family history of prostate cancer, *n* (%) [b] | 55 (27) | 79 (29) | 42 (27) | 0.89 |
| BMI, mean (SD) | 28.2 (4.3) | 27.6 (4.0) | 28.4 (5.0) | 0.08 |

ANOVA = analysis of variance; BMI = body mass index; IQR = interquartile range; PSA = prostate-specific antigen; SD = standard deviation.
[a] *p* values comparing biopsy outcomes from the first surveillance biopsy (no cancer, cancer without reclassification, or reclassification), from chi-square test for categorical variables and from ANOVA for continuous variables. For prostate volume, PSA, PSA density, core ratio, and *p* value from Kruskal–Wallis test.
[b] Core ratio missing for 38 participants and family history of prostate cancer missing for 21 participants.




Log-rank test $p < 0.001$

Number at risk:

| | Time since Bx1 (yr) | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** | **5** |
| **Bx1–** | 214 | 176 | 132 | 90 | 40 | 18 |
| **Bx1+** | 282 | 196 | 132 | 82 | 41 | 12 |

**Fig. 2 – Time to grade and/or tumor volume reclassification by first surveillance biopsy outcome. Bx1 = first surveillance biopsy; Bx1– = no cancer detected on first surveillance biopsy; Bx1+ = cancer but no reclassification detected on first surveillance biopsy.**

All results were similar when sensitivity analysis was performed for grade-only reclassification or for the subset of participants diagnosed with Gleason 3 + 3 cancer, and can be found in the Supplementary material. Prior biopsy result was not found to be associated with biopsy timing in an adjusted analysis. Similar significance was observed in a sensitivity analysis that minimized potential ascertainment bias (see the Supplementary material for more details).

## 4. Discussion

Our present study examined the risk of pathological reclassification in AS patients who have no cancer on first or second surveillance biopsy. In both Kaplan–Meier and multivariable-adjusted Cox proportional hazard analyses, no cancer on surveillance biopsy was prognostic against future reclassification. When there was no detectable

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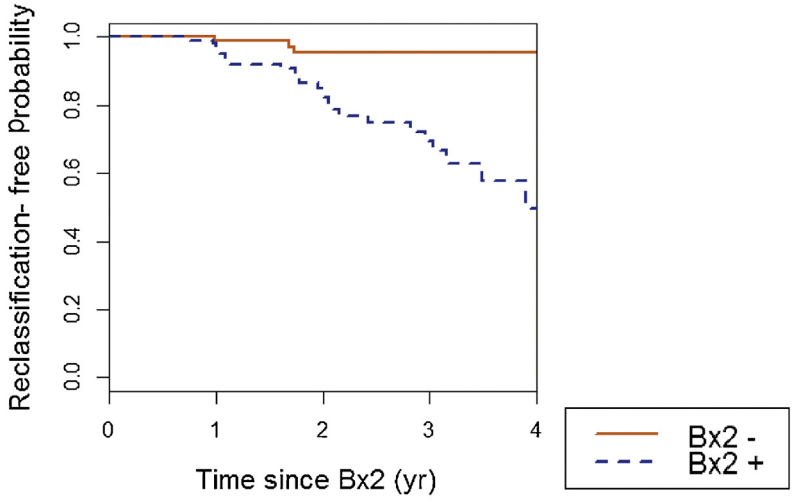


Log-rank test $p < 0.001$

Number at risk:

| | Time since Bx2 (yr) | | | | |
|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** |
| **Bx2–** | 120 | 88 | 55 | 26 | 10 |
| **Bx2+** | 139 | 98 | 57 | 26 | 5 |

**Fig. 3 – Time to grade and/or tumor volume reclassification by second surveillance biopsy outcome. Bx2: second surveillance biopsy; Bx2–: no cancer detected on second surveillance biopsy; Bx2+:cancer but no reclassification detected on second surveillance biopsy.**

**Table 2 – Time to grade and/or tumor volume reclassification, from time of first surveillance biopsy (*n* = 494 [a], 85 with event)**

| Variable | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CI) [b] | *p* value [b] | HR (95% CI) [b] | *p* value [b] |
| No cancer on first surveillance biopsy (vs cancer without reclassification) | 0.44 (0.27, 0.71) | <0.001 | 0.50 (0.30, 0.83) | 0.008 |
| Ln (PSA on/prior to first surveillance biopsy) | 1.93 (1.32, 2.83) | <0.001 | 2.74 (1.83, 4.10) | <0.001 |
| Ln (prostate volume, cc) | 0.38 (0.22, 0.69) | 0.001 | 0.19 (0.10, 0.37) | <0.001 |
| BMI | 1.03 (0.98, 1.09) | 0.28 | 1.07 (1.01, 1.13) | 0.02 |

BMI = body mass index; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
[a] Two participants were missing core ratio data and were not included in the modeling.
[b] 95% confidence intervals and *p* values from Cox proportional hazards models.

**Table 3 – Time to grade and/or tumor volume reclassification, from the time of second surveillance biopsy (*n* = 259, 29 with event)**

| Variable | Univariable | | Multivariable | |
|---|---|---|---|---|
| | HR (95% CI) [a] | *p* value [a] | HR (95% CI) [a] | *p* value [a] |
| No cancer on second surveillance biopsy (vs cancer without reclassification) | 0.12 (0.03, 0.39) | <0.001 | 0.18 (0.05, 0.66) | 0.01 |
| No cancer on first surveillance biopsy (vs cancer without reclassification) | 0.35 (0.15, 0.82) | 0.02 | 0.53 (0.20, 1.41) | 0.20 |
| Ln (PSA on/prior to second surveillance biopsy) | 4.66 (2.22, 9.78) | <0.001 | 6.10 (2.62, 14.17) | <0.001 |
| Ln (prostate volume, cc) | 0.45 (0.16, 1.26) | 0.13 | 0.18 (0.05, 0.64) | 0.008 |

CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
^ 95% confidence intervals and p-values from Cox proportional hazards models.

cancer in the first surveillance biopsy, the risk of future reclassification was decreased by 50%, and if no cancer was seen on second surveillance biopsy, then there was an 82% decreased risk of future reclassification.

We also found that patients with no cancer on first surveillance biopsy were more likely to have no cancer on the second surveillance biopsy when compared with those who had a first surveillance biopsy with cancer but no reclassification. This is consistent with previous work suggesting that no cancer found on initial surveillance biopsy is protective against future reclassification [8–11] and work suggesting that negative biopsy prior to diagnosis

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is associated with lower adverse pathological outcomes at radical prostatectomy [12]. Importantly, it also appears that continued presence of cancer on subsequent surveillance biopsy results in a significantly higher risk of pathological reclassification. Within 5 yr of diagnosis, ~3–5% of patients with no cancer on surveillance biopsies reclassify compared with ~20–30% of those who have some cancer on subsequent biopsies. These findings indicate that even in men who do not initially reclassify, there is a persistent risk of pathological reclassification and thus a need for continued surveillance. Decreasing risk of reclassification with increasing biopsy number was seen in this cohort, with 25% of men reclassifying on first biopsy and 17% reclassifying on second biopsy. This is consistent with our previously reported data and other AS cohorts that demonstrate decreasing rates of reclassification over time [3,7,13–15].

One of the major goals of evaluating factors that predict reclassification of prostate cancer on AS is to use all available data in the best possible manner to decrease the number of prostate biopsies required without sacrificing the detection of potentially lethal prostate cancer. Laviana et al [4] found that the economic cost of AS increases steadily with time, surpassing the cost of brachytherapy within 9 yr and nearly equaling that of robotic-assisted laparoscopic prostatectomy by 12 yr. These costs were driven chiefly by serial prostate biopsy. In addition to the financial cost of biopsies, there are biopsy-related morbidities, most notably an approximately 5% risk of infection [5]. However, as seen in the ProtecT trial, a strategy of "active monitoring" that relies solely upon large increases in serum PSA levels to trigger prostate biopsy may be an inadequate paradigm, with a 2.6-time increased risk of clinical progression [16]. One or more mandatory surveillance biopsies are likely necessary to better risk stratify patients before making decisions regarding future biopsy frequency. Using a finding that is prognostic against reclassification, such as surveillance biopsy without cancer, to decrease biopsy frequency may decrease patient discomfort, cost, and risk of infection while maintaining detection of significant disease.

In order to best use available clinical information, it is worth noting that the risk of reclassification associated with a given variable changes depending on what has transpired with the patient during his course of surveillance. Previously published nomograms for reclassification while on AS [17,18] do not adjust their covariates over the course of AS, despite patients having different risk profiles as they undergo biopsies without reclassification. We found that no cancer on second surveillance biopsy was much more prognostic against reclassification than no cancer on the first surveillance biopsy (HR 0.18 vs 0.50). This finding is consistent with previous reported outcomes where fewer men reclassify on AS over time [10]. Given that clinical variables may confer different risks at different time points, models and risk assessment tools should account for these varying risks.

The major strengths of our study include the fact that it is a multicenter, prospectively designed study with quality control of all clinical data collected. All participants were recommended the same biopsy schedule (6–12 mo after diagnosis, 24 mo after diagnosis, and then every 2 yr), regardless of whether or not they had detectable disease on surveillance biopsies. Overall, 80% of biopsies were per protocol (on time), and finding no cancer in the first surveillance biopsy was not associated with delayed subsequent biopsies. The inclusion at diagnosis of both Gleason 3 + 3 and 3 + 4 disease makes the results more generalizable to community AS protocols. In addition, the use of pathological reclassification as the end point does not rely upon patient factors such as tolerance for risk or anxiety that may sway treatment decisions. The study is limited by the lack of a centralized pathological review, lack of information for all patients regarding MRI use in the surveillance of these men, and relatively small numbers of patients with long-term follow-up. These limitations are mitigated by the fact that an early central pathology review indicates ~80% concordance with local pathology scoring, and most patients in PASS have not had prostatic MRI. Additionally, MRI is still not considered the standard of care in AS according to National Comprehensive Cancer Network guidelines [19]. Inclusion of more patients over time with similar risk profiles would be expected to tighten the confidence intervals rather than significantly change hazard ratios. In addition, our study would benefit from validation by an external AS cohort.

## 5. Conclusions

No detectable cancer in a biopsy during AS was prognostic for a decreased risk of pathological reclassification. The clinical impact of no cancer on surveillance biopsy becomes stronger on subsequent biopsy, suggesting that the risk of reclassification changes with time. Men with Gleason 3 + 3 prostate cancer and two initial surveillance biopsies with no detectable cancer may not warrant annual or semiannual biopsy, and may perhaps lengthen the biopsy interval to several years, similar to other published protocols [3]. Further work with models should include the concept of varying risk by taking into account real-time variables along the course of AS in order to individualize biopsy intervals and patient assessments. Portions of this work were presented as a moderated poster at the AUA Annual Meeting, May 2017.

***Author contributions:*** James T. Kearns had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Kearns, Faino, Newcomb, Zheng, Lin.
*Acquisition of data:* Brooks, Carroll, Dash, Ellis, Fabrizio, Gleave, Morgan, Nelson, Thompson, Wagner, Lin.
*Analysis and interpretation of data:* Kearns, Faino, Newcomb, Zheng, Lin.
*Drafting of the manuscript:* Kearns, Faino, Newcomb, Zheng, Lin.
*Critical revision of the manuscript for important intellectual content:* All authors.
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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.01.016.

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