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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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