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Prostate Cancer

# Predictors of Pathologic Progression on Biopsy Among Men on Active Surveillance for Localized Prostate Cancer: The Value of the Pattern of Surveillance Biopsies

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**Abstract**

***Background:*** A better understanding of the independent predictors of disease progression for prostate cancer (PCa) patients is needed to improve the selection of ideal candidates for active surveillance (AS) and refine the surveillance regimen.
***Objective:*** To examine the association of clinical and pathologic characteristics, as well as patterns of surveillance biopsy results, with the risk of progression in men on AS.
***Design, setting, and participants:*** The retrospective study consisted of men with PCa who were on AS in the prospectively maintained University of California, San Francisco, institutional database from 1996 to 2011. Strict criteria for AS were prostate-specific antigen (PSA) $\leq$10 ng/ml, clinical stage T1 or T2, biopsy Gleason grade 6, <33% positive cores, and <50% tumor in any single core. Men were then categorized based on results of their confirmatory surveillance biopsy.
***Outcome measurements and statistical analysis:*** *Disease progression* was defined as an increase in Gleason grade and/or biopsy volume beyond prespecified cut points. Serial biopsy patterns over the course of surveillance were stratified by confirmatory biopsy findings: negative, positive without progression, and positive with progression. Multivariable logistic regression models were used to evaluate predictors of progression during AS.
***Results and limitations:*** A total of 465 men met inclusion criteria (median follow-up: 51 mo). Of these men, 23% had negative confirmatory biopsies. Only 3% of the men (1 of 30) progressed by the fourth surveillance biopsy following a biopsy pattern of negative confirmatory and negative third biopsy findings. Negative confirmatory biopsy and lower PSA density (both $p < 0.01$) were independently associated with decreased odds of biopsy progression at 3 yr. The main limitation of this study is its observational nature.
***Conclusions:*** The patterns of surveillance biopsy results yield additional important information in AS. Negative confirmatory biopsy and PSA density are important independent predictors of progression on AS and may be used to better counsel men opting for AS.

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## 1. Introduction

Prostate cancer (PCa) is the most common malignancy in the United States, with an estimated incidence of 238 590 cases in 2013 [1]. In the prostate-specific antigen (PSA) era, a significant proportion of these incident cases fall into the low-risk category, as defined by the D'Amico criteria [2,3]. This situation has led to the development of active surveillance (AS) programs by many institutions [4]. As a result of this work, AS has become a widely accepted management strategy for men with low-grade, low-volume, localized PCa, and such an approach is supported by the practice guidelines of several national organizations. The apparent safety of AS has been demonstrated by single-institution series with intermediate follow-up, although the long-term safety of AS is still to be determined [4–7].

While the eligibility criteria for entry into AS protocols vary around the world, AS has by and large proven to be an alternative for carefully selected men with low-risk, localized PCa [8,9]. As more men are placed on AS programs, it is appealing to identify the means to limit the number of prostate biopsies over time, as well as to identify men with truly low risk of disease progression. Substantial efforts to identify genetic and genomic markers [10,11] and newer imaging modalities such as multiparametric magnetic resonance imaging are promising [12], although their role in AS currently requires more study and validation.

Improving risk prediction allows men at low risk of progression to undergo less intense surveillance (ie, prostate biopsy) regimens and provides more accurate risk assessment at the initiation of AS. Toward this end, we sought to determine the association of clinical and biopsy characteristics with the risk of progression in men enrolled in the AS program at the University of California, San Francisco (UCSF).

## 2. Methods

Strict diagnostic criteria for AS at UCSF are PSA $\leq$10 ng/ml, clinical stage T1 or T2 and biopsy Gleason grade 3 + 3, <33% positive cores, and <50% tumor in any single core. Men on AS between 1996 and 2011 who consented to prospective data collection with no active treatment for $\geq$6 mo were identified for the current study. Each patient underwent a confirmatory biopsy following a diagnostic biopsy. All subsequent biopsies were considered surveillance biopsies. In addition to men meeting AS criteria, 31 men with Gleason grade $\geq$7 disease were also enrolled because of either low-volume Gleason 3 + 4 disease or patient preference; 41 men with diagnostic PSA values >10 ng/ml were also included because of having either low-volume disease or patient preference. The institutional review board of UCSF approved this study.

All biopsies included $\geq$10 cores. Diagnostic biopsies done outside UCSF underwent slide re-review. Surveillance after diagnosis consisted of quarterly PSA testing, semiannual digital rectal examination, and transrectal ultrasonography (TRUS), with confirmatory biopsies recommended within 12 mo of diagnostic biopsy. Surveillance biopsies then were recommended every 12–24 mo based on previous biopsy and imaging results. Patients in the latter 2 yr of the study also began receiving magnetic resonance imagining (MRI) of the prostate following initial diagnosis.

To examine serial biopsy result patterns over the course of surveillance, patients were stratified by a positive, negative, or progression confirmatory biopsy result. Outcome patterns of subsequent surveillance biopsies are reported. Biopsy cores were taken from each sextant and included anterior gland sampling. *Biopsy progression* was defined as an upgrade of the primary or total score to 3 + 4 or higher (eg, 3 + 3 to any pattern 4, 3 + 4 to 4 + 3), an increase in volume to >33% positive cores and/or >50% of a single core. No patient progressed by imaging (ie, TRUS, MRI, or both) or by digital rectal examination.

Patients were categorized based on positive compared with negative confirmatory biopsy, defined as the first biopsy following the diagnostic biopsy. Means and frequency tables were used to describe demographics (age, race/ethnicity, relationship status) and diagnostic PSA, PSA density, Gleason grade, number of biopsy cores taken and percentage positive, and Cancer of the Prostate Risk Assessment (CAPRA) clinical risk score [13]. The *t* test and the Pearson chi-square test were used to compare demographic and clinical characteristics of the biopsy groups, as appropriate.

Odds of biopsy progression were evaluated by multivariable logistic regression adjusted for negative confirmatory biopsy, age, and clinical characteristics (PSA density, clinical tumor stage, and percentage of positive biopsy cores). Multivariable regression models were used to evaluate the association between negative confirmatory biopsy and subsequent progression in two subsets: men with at least three biopsies and 3 yr of follow-up ($n$ = 242; model 1) and men with at least four biopsies and 4 yr of follow-up ($n$ = 131; model 2). Model 2 replaces the covariate negative confirmatory biopsy with negative confirmatory and negative third surveillance biopsy to assess the association of this biopsy pattern with biopsy progression. Model covariates were assessed for inter-item correlations. PSA density was not normally distributed and therefore was modeled as the log of PSA density. Sensitivity analyses were conducted on subgroups that strictly met AS criteria to assess differences in magnitude of effect. A $p$ value <0.05 was considered significant. All analyses were performed using SAS 9.2 for Windows (SAS Institute, Cary, NC, USA).

## 3. Results

As of January 2013, 957 men were enrolled in AS at UCSF. To date, 731 men have consented to participate in research, with 593 men having undergone at least one repeat biopsy. Of those men, 465 had $\geq$10 diagnostic biopsy cores taken and formed the final cohort for this study. Seventy-six percent of the final cohort met strict diagnostic criteria for AS, compared with 45% of those AS men not included. The mean age was 61.7 yr (standard deviation: 7.55), the median PSA was 5.1 ng/ml (interquartile range [IQR]: 3.9–6.8), and the median percentage of positive cores was 10% (IQR: 7–17%). The median year of diagnosis was 2006 (IQR: 2004–2009), and median follow-up after diagnosis was 51 mo (range: 9–177) (Table 1).

Nearly one-quarter of the final cohort ($n$ = 108, 23%) had negative confirmatory biopsies, and the remainder ($n$ = 357, 77%) had positive confirmatory findings (Table 1). The median time to confirmatory biopsy was 12 mo (IQR: 7–17), with 66 men biopsied >24 mo after diagnosis. The negative and positive confirmatory biopsy groups did not differ by time to biopsy, mean age, race/ethnicity, relationship status, PSA at diagnosis, clinical T stage, diagnostic Gleason score, mean number of diagnostic biopsy cores taken, or CAPRA risk. However, men with negative confirmatory biopsies had a lower mean percentage of positive cores (9.7%) compared with men with positive findings (14.7%) ($p < 0.01$). Thirty-eight percent of men had two biopsies, and 62% had three

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