A Negative Confirmatory Biopsy Among Men on Active Surveillance for Prostate Cancer Does Not Protect Them from Histologic Grade Progression

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Abstract

Background: Many men (21–52%) are reported to have no cancer on the second, also known as the confirmatory, biopsy (B2) for prostate cancer active surveillance (AS). If these men had a reduced risk of pathologic progression, particularly grade related, the intensity of their follow-up could be decreased.

Objective: To investigate if men with no cancer on B2 are less likely to undergo subsequent pathologic progression.

Design, setting, and participants: Men were identified from our tertiary care center AS prostate cancer database (1995–2012). Eligibility criteria were prostate-specific antigen (PSA)/C20 ≤ 10, cT2 or lower, no Gleason grade 4 or 5, three or fewer positive cores, and no core >50% involved. Only patients with three or more biopsies were selected and then dichotomized on cancer status (yes or no) at B2.

Intervention: AS.

Outcome measurements and statistical analysis: Pathologic progression was defined as grade (advancement in Gleason score) and/or volume (more than three positive cores, >50% core involved). Progression-free survival was compared. Predictors of progression were investigated using a Cox proportional hazards model.

Results and limitations: Of the 286 patients remaining on AS after B2, 149 (52%) had no cancer and 137 (48%) had cancer. The median follow-up after B2 was 41 mo (interquartile range [IQR]: 26.5–61.9). Progression-free survival at 5 yr was 85.2% versus 67.3% for negative B2 versus cancer on B2, respectively (p = 0.002). Men with no cancer at B2 had a 53% reduction in risk of subsequent progression (hazard ratio [HR]: 0.47; 95% confidence interval [CI], 0.29–0.77; p = 0.003). Subanalysis showed prognostic indicators of volume-related progression were absence of cancer (HR: 0.36; 95% CI, 0.20–0.62; p = 0.0006) and PSA density (HR: 1.79; 95% CI, 1.12–2.89; p = 0.01). The only predictor of grade-related progression was age (HR: 1.05; 95% CI, 1.00–1.10; p = 0.04). Retrospective analysis was the major limitation of the study.

Conclusions: Absence of cancer on B2 is associated with a significantly decreased risk of volume-related but not grade-related progression. This must be considered when counseling men on AS.

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1. Introduction

As active surveillance (AS) for low-risk prostate cancer gains acceptance, we require improvements in risk assessment to counsel individual patients regarding prognosis [1,2]. Currently, patients undergo repeat prostate biopsies to monitor for progression and account for sampling error, although the frequency of rebiopsy reported in the literature ranges from yearly [3] to every 3–4 yr [4]. Stratification to guide intensity of follow-up would be desirable to avoid biopsy-related morbidity [5,6] without compromising the detection of significant progression.

An easily identifiable group where frequency of rebiopsy might be reduced is men with absence of cancer on their confirmatory, or second, AS biopsy (B2). A review of published AS cohorts found this ranged from 21% to 52% [1]. This phenomenon most likely arises both from selecting men with low-volume disease and the inherent sampling error associated with transrectal ultrasound-guided prostate biopsy (TRUSPB) [7]. The absence of cancer on prostate rebiopsy is comforting for both patient and physician, and intuitively it would suggest a lower risk of progression.

We investigated the prognostic significance of a negative confirmatory AS biopsy on pathologic progression in an AS cohort. Because absence of cancer is likely a surrogate marker for extremely low-volume disease, we also examined potential predictors of grade- and volume-defined progression.

2. Patients and methods

Patients were identified from the AS database at Princess Margaret Cancer Centre (PMCC) between 1995 and 2012. This is a prospectively maintained database approved by the research ethics board. Eligibility criteria were patients with prostate-specific antigen (PSA) <10, clinical stage T2a or lower, no Gleason grade 4 or 5, three or fewer positive cores (PCore) involved, and no core >50% involved at the diagnostic biopsy.

For the purposes of this study, we defined the first (base-line, diagnostic) TRUSPB as biopsy 1 (B1) and the second biopsy (confirmatory, first AS or repeat biopsy) as biopsy 2 (B2). Patients who did not receive a third (B3) or subsequent biopsy, because of either stopping AS after B2 or having insufficient follow-up to reach B3, were excluded (Fig. 1). Thus patients who progressed (or were reclassified) at B2 and ceased AS were excluded from this study. The remaining patients who continued with AS (n = 286) were dichotomized on the basis of cancer status (yes or no) from B2. The primary outcome analyzed was pathologic progression, occurring at any biopsy, after B2. Pathologic progression was defined as an increase in Gleason score (GS) ≥7 (grade-related progression) and/or volume-related progression (PCore more than three or single core maximum involvement >50%).

Three genitourinary radiologists performed TRUSPB, and a single operator (A.T.) performed the majority (75%). A standard extended 10- to 12-core template schema was used for initial biopsy, with a 13- to 17-core Babaian schema [8] performed for repeat biopsies after 2001. All biopsies taken at PMCC were read by one of four dedicated genitourinary pathologists, and synoptic reporting was used. Although a standardized follow-up protocol is not used at PMCC, patients are generally reviewed with PSA and digital rectal examination (DRE) every 3 mo for 2 yr and then every 6 mo if stable. A confirmatory biopsy is recommended to patients within 12 mo of initial diagnostic biopsy and then every 1–3 yr until the patient reaches 80 yr of age or declines active treatment. Earlier biopsy is triggered by either a rising PSA or an abnormal DRE at the treating physician’s discretion. Magnetic resonance imaging (MRI) was performed selectively, often if there was a discrepancy between PSA and biopsy findings, to examine for an anterior tumor [9].

Differences between groups were determined by the independent t test or the chi-square test. Univariate and multivariate Cox proportional hazards regression were used to examine absence of cancer and other standard clinical parameters for predictors for progression.

Subanalyses for predictors of both grade-related and volume-related progression were also performed. Grade-related progression was defined as men with grade-only and grade-and-volume progression. Volume-related progression included men with volume-only and volume-and-grade progression. Important clinical and pathologic variables for the Cox regression analysis were selected and univariate analysis performed to identify significant variables. The number of covariates for the multivariable model was selected to avoid overfitting and a collinearity check performed for PSA, prostate volume, and PSA density (PSAD), with PSAD carried forward into the multivariable model.

Progression-free probability estimates were calculated by the Kaplan-Meier method and comparisons made by the log-rank test.

Survival time began at the date of B2, and patients were censored at the time of progression biopsy, time of treatment, or date of last follow-up. Logistic regression was performed to identify predictors at baseline for absence of cancer on B2 and the model assessed with the C statistic and Hosmer-Lemeshow goodness-of-fit test. All statistical tests were two sided with p < 0.05 considered statistically significant. SAS statistical software v.9.1 (Cary, NC, USA) was used for all analyses.

3. Results

Of the total 286 patients remaining on AS after B2 and available for analysis, 149 (52%) had no cancer and 137 (48%) had cancer. The overall median follow-up after B2 was 41 mo (interquartile range [IQR]: 26.5–61.9). For both groups, there was no difference between the median number of TRUSPBs performed after B2 or the time interval from B2 to subsequent biopsies. Table 1 shows a comparison of characteristics at the time of B2 between the no-cancer and cancer groups. Significant differences noted between the groups were age, PSA, and prostate volume, although PSAD was similar. Approximately 60% of men in
both groups had their B2 performed ≤12 mo after B1, and 92.5% of men had >10 cores taken at B2. There were 19 patients excluded from analysis who stopped AS after B2 without pathologic progression and thus never had B3. Of these men, 17 elected to have active treatment without pathologic progression, and 2 had their B3 within 3 mo of B2.

Table 2 shows pathologic progression and important related variables. The number of men with pathologic progression differed significantly between the no-cancer and cancer groups (23.5% vs 40.1%, respectively; \( p = 0.002 \)). When examining for differences in type of progression, men with cancer at B2 were more likely to have volume-related progression than those without (29.2% vs 12%; \( p = 0.0003 \)). The frequency of grade-related progression for both groups was similar (no cancer 17.5% and cancer 23.4%; \( p = 0.12 \)) with most having a GS 3 + 4.

The probability of remaining free of pathologic progression, stratified by cancer status at B2, is shown in Figure 2a. Median time to progression was 32.5 mo (IQR: 19.9–56.9 mo) for the no-cancer group and 26.9 mo (IQR: 17.5–37.3 mo) for the cancer group (log-rank \( p = 0.002 \)). The probability of remaining free of pathologic progression at 5 yr, stratified by cancer status on B2, was 85.2% (no cancer) and 67.3% (cancer) (\( p = 0.003 \)). Kaplan-Meier survival curves for both grade-related and volume-related progression, stratified by cancer status at B2, are shown in Figure 2b and 2c. A significant difference between groups is seen with volume-related progression-free survival (\( p < 0.001 \)) but not with grade-related progression (\( p = 0.07 \)).

Univariate and multivariate Cox regression analysis for predictors of progression at B3 or subsequent biopsies is
shown in Table 3. On multivariate analysis, no cancer at B2 was associated with a 53% reduction in risk of progression (hazard ratio [HR]: 0.47 [0.29–0.77]; \( p = 0.003 \)). In addition, increasing age (HR: 1.05 per year [1.01–1.09]; \( p = 0.01 \)), PSA density (PSAD) (HR: 1.49 per unit increase [1.02–2.18]; \( p = 0.041 \)), and MRI reporting cancer (HR: 1.74 [1.00–3.01]; \( p = 0.049 \)) were predictors of progression.

Subanalyses examining for predictors of volume-related (\( n = 58 \)) and grade-related (\( n = 58 \)) progression were performed. Prognostic variables for volume-related progression were cancer status at B2 (HR: 2.78; 95% confidence interval [CI], 1.61–5.0; \( p = 0.006 \)) and increasing PSAD (HR: 1.49 per unit increase [1.02–2.18]; \( p = 0.041 \)), and MRI reporting cancer (HR: 1.74 [1.00–3.01]; \( p = 0.049 \)) were predictors of progression.

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pathologic progression, subclassified into grade- and volume-related progression.

Our findings demonstrated that absence of cancer on B2 was associated with a 54% decreased risk of subsequent pathologic progression (HR: 0.46; \( p = 0.002 \)), with a significant difference in 5-yr progression-free survival after B2 (Fig. 2) between the no-cancer and cancer groups (85.2% vs 67.3%; log-rank \( p = 0.002 \)). Cancer status at B2 was reported previously as a predictor of progression\[15–17\]. Al-Otaibi et al.\[15\] suggested a difference in the 5-yr actuarial progression-free probability of 82% (negative B2) compared with 50% (positive B2), although this cohort was small (\( n = 92 \)) with only 50 men having two or more AS biopsies. Both Adamy et al.\[17\] and Tseng et al.\[16\] found on multivariate analysis that cancer status at B2 was a predictor of progression.

Previous studies on AS have not differentiated between grade- and volume-related progression. We found a significant difference in volume-related progression between the no-cancer and cancer groups (12.1% vs 29.2%; \( p = 0.0003 \)), whereas grade-related progression was similar (17.5% vs 23.4%; \( p = 0.12 \)). Cancer status at B2 and increased

![Fig. 2](image-url)
PSAD predicted volume-related progression; increasing age predicted grade-related progression. Because men with no cancer at B2 represent one end of the spectrum of low-volume disease, it is not surprising that they are less likely to progress on volume criteria. Importantly, grade-related progression still occurred in the no-cancer group (17.5%), so biopsy cannot be completely abandoned. The differences in grade- and volume-related progression found in our study have implications for the reporting of pathologic progression in AS. Institutional variations in volume-related eligibility parameters mean the definitions of progression will also differ [16–18]. We suggest that grade-related progression should be reported independently of total progression because GS 6 remains the most consistent inclusion criteria used across institutions [3,4,17,19–21].

The understanding of volume progression as a trigger for treatment in AS is poor and reflected in the uncertainty seen in various guidelines. Currently, only the National Institutes of Health (NIH) consensus statement specifically includes volume by stating, “increased extent of disease (more biopsy tissues involved with cancer)” [11]. The European Association of Urology (EAU) guidelines list “Gleason score ≥7, patient anxiety, and PSA doubling time” [22]. The National Comprehensive Cancer Network states, “change in risk group strongly implies disease progression” [23]. The National Institute for Health and Clinical Excellence suggests “rise in PSA or adverse findings on biopsy” [24].

Other than cancer status at B2, significant predictors of pathologic progression identified were increasing age, PSAD, and cancer seen on MRI (Table 3). Age, the only predictor of grade-related progression, is a well-established risk factor for high-grade prostate cancer [25]. PSA and PSAD were reported previously as predictors of progression [16,17] and time to active treatment [16,26]. Both the EAU and NIH guidelines recommend the use of PSAD to guide triggering treatment [11,22].

The role of multiparametric MRI to select patients for AS [27] and predict high-risk disease or progression [14] is still under investigation. Most published series are retrospective, and expertise currently remains restricted to certain centers, limiting generalizability. Our results regarding MRI predicting progression should be interpreted cautiously because MRI was used selectively, usually to investigate for anterior tumors when there was a discordance between PSA and biopsy findings [9]. There may be a role for MRI to increase sensitivity of biopsy in low-volume disease and guide timing of rebiopsy, although the costs of MRI would need to be balanced against the morbidity of TRUSPB.
alternative technique to MRI for the detection of anterior tumors is transperineal template-guided mapping prostate biopsy (TTMB).

Evaluation of TTMB to diagnose prostate cancer, in the setting of previous negative TRUSPB, found cancer detection rates of 34.4–55.5%. With increasing previous negative biopsies, cancer was identified more frequently in the anterior part of the prostate [28].

Although our analysis is limited by length of follow-up, the median follow-up (41 mo; IQR: 26.5–61.9) is comparable with published contemporary series [3,4,17,19–21]. With short follow-up in a disease having a long natural history, it is difficult to ascertain the relationship between pathologic progression and longer-term outcomes. However, pathologic progression is important because it often triggers treatment with its associated morbidity. By restricting our cohort to having three or more AS biopsies, generalizability is limited to men who are on AS for longer periods of time. Although our institution has a guide to biopsy every 1–3 yr, there is variation in follow-up intensity reflected in the timing of surveillance biopsies. In our cohort, 25% of men had B2 12–24 mo after B1, with a further 10% >24 mo. This may differ with other AS series. However, analyses showed that the total number of biopsies performed and the time from B2 to subsequent biopsies was similar between the two groups (Table 2). An important point to recognize is that the timing of the diagnosis of progression is limited by the timing of prostate biopsies. Part of our cohort has been used for previous studies examining the effect of 5-ARI on progression in men on AS [10,29]. However, it should be noted that both previous studies included men who progressed at B2, unlike the current cohort under investigation, and hence the risk and time point of progression is different. In our cohort, 82.3% had >12 cores taken at B2. Occasionally, a Babaian template may consist of fewer than 13–17 cores because in smaller glands the peripheral and transition zones are sampled in a single needle firing. However, undersampling is possible but was balanced between our groups. Our cohort spanned a change in GS grading (2005). However, the total number of patients affected by this time period was relatively small (before 2005, n = 48 [16.8%]) and was evenly distributed between our two groups (Table 1). Biopsy specimens were evaluated by four dedicated genitourinary pathologists, and even in a high-volume center with a centralized review of difficult cases, interobserver variation may still be present.

5. Conclusions

At our institution, absence of cancer at B2 was a significant protective factor for pathologic progression, decreasing its risk by 53%. However, our subanalyses suggest further investigation is required because cancer status at B2 and PSAD were found to be prognostic factors for volume-related progression, whereas only increasing age predicted grade-related progression. Thus subsequent biopsy in men with negative B2 cannot be completely abandoned or delayed at present, and clinicians should avoid being overly reassured by the absence of cancer at B2. As AS cohorts mature, the long-term significance of both grade- and volume-related progression will emerge.

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Author contributions: Antonio Finelli 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: Wong, Finelli, Trottier, Margel.

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Appendix A. Supplementary data

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References


