An Increase in Gleason 6 Tumor Volume While on Active Surveillance Portends a Greater Risk of Grade Reclassification with Further Followup

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Purpose: We evaluated the relative risk of later grade reclassification and outcomes of patients in whom high volume Gleason 6 prostate cancer develops while on active surveillance.

Materials and Methods: A prospectively maintained database was used to identify patients on active surveillance between 1998 and 2013. Tumor volume was assessed based on the number of positive cores and proportion of core involvement. The chi-square and Fisher exact tests were used for analysis as appropriate. The primary end point was the development of grade reclassification, defined as grade only and/or grade and volume at the event biopsy.

Results: A total of 555 men met the study inclusion criteria. Mean followup was 46 months. Overall 70 patients demonstrated an increase in tumor volume at or after biopsy 2. Compared to those men never experiencing volume or grade reclassification, prostate specific antigen at diagnosis was not significantly different ($p=0.95$), but median prostate volume was smaller in patients who demonstrated volume reclassification ($p <0.001$). The incidence of pure volume reclassification was 6.8%, 6.1% and 7.8% at biopsy 2, 3 and 4, respectively. Men with volume reclassification were more likely to experience later grade reclassification than those without at 33.3% vs 9.3%, respectively ($p <0.0001$).

Conclusions: While Gleason 6 prostate cancer has a favorable natural history, it appears that patients on active surveillance who experience volume reclassification are at substantially higher risk for grade reclassification. Thus, urologists should pay close attention to tumor core involvement, and monitoring should be adjusted accordingly for early volume reclassification in younger men and those in good health.

Key Words: prostatic neoplasms, tumor burden, neoplasm grading, biopsy, watchful waiting

Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor
AS = active surveillance
B1 = diagnostic biopsy (biopsy 1)
B2 = confirmatory biopsy (biopsy 2)
B3 = biopsy 3 (from diagnostic)
B4 = biopsy 4
GS = Gleason score
PCa = prostate cancer
PSA = prostate specific antigen

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While prostate cancer is the most common malignancy affecting men, approximately 80% of men with PCa ultimately die of other causes.[1–3] A significant proportion of incident cases are classified as low risk PCa according to the D'Amico criteria and, thus, do not necessitate immediate radical treatment.[4,5] To mitigate overtreatment of indolent PCa many institutions have adopted active surveillance programs.[1] In recent years

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AS has become a widely accepted management strategy for men with low grade, localized PCa, with strong support for its use from the practice guidelines of several national organizations.[2]

The safety of AS has been demonstrated by single institution series with intermediate followup.[3] However, the long-term verdict for AS has not been well established.[6–9] Current practice protocols combine clinical T-stage, PSA value, PSA density, Gleason score, number of positive cores and/or amount of malignancy per core to select patients for AS.[9,10] While AS has by and large proven to be a good alternative for carefully selected men with low risk PCa,[11,12] there is a lack of understanding concerning indicators of progression and what is considered clinically significant progression. As more men are placed on AS programs it becomes important to identify these indicators.

Commonly GS upgrading to 7/10 or greater on routine biopsy will trigger treatment in a patient on AS. Increasing PSA and tumor volume are also indicators that can prompt physicians to offer therapy. However, increasing tumor volume as a prompt for treatment is not well-defined. Currently only the National Institutes of Health consensus statement specifically includes volume as a factor, with "increased extent of disease (more biopsy tissues involved with cancer)."[8] The European Association of Urology guidelines list "GS $\geq$7, patient anxiety and PSA doubling time" as indicators of progression and reasons to offer treatment.[13] The National Comprehensive Cancer Network states, "change in risk group strongly implies disease progression,"[14] and the National Institute for Health and Care Excellence suggests, "rise in PSA or adverse findings on biopsy" should trigger definitive treatment for men with PCa.[15]

This lack of consensus stems in part from the variability of AS inclusion criteria. Some protocols specify the number of positive cores involved whereas others may only indicate a proportion of total cores. The definition of volume progression is further complicated by the contended prognostic value of tumor volume.[15–17] A contemporary study showed that in men suitable for AS who underwent up-front RP, the number of positive cores at biopsy predicted the presence of higher grade and stage disease at final pathology.[18,19] In this study we determine the association of increased tumor volume after diagnostic biopsy with the risk of later grade reclassification in men enrolled in an AS program.

METHODS

Men diagnosed with low risk PCa and started on AS were identified using the Princess Margaret Cancer Centre AS database (1998 to 2013). Approval from the institutional ethics review board was obtained. AS eligibility criteria were PSA 10 ng/ml or less, clinical stage cT2 or less, GS 6 or less, number of positive cores 3 or less, no single core more than 50% involved, age 75 years or less and at least 1 repeat prostate biopsy after diagnosis (confirmatory, B2). For the purposes of this study we defined the first (diagnostic) transrectal ultrasound guided prostate biopsy as biopsy 1 (B1) and the second biopsy (confirmatory) as biopsy 2 (B2). Patients undergo a confirmatory biopsy within 12 to 24 months of the initial biopsy, with repeat biopsy every 1 to 3 years until the patient reaches age greater than 75 years or declines definitive treatment.

Patients who did not meet the AS criteria, those who did not undergo a confirmatory biopsy (B2) or those who did not have sufficient followup to reach B2 were excluded from analysis. The remaining patients on AS (518) were grouped based on reclassification (yes or no) and type of reclassification (volume or grade reclassification only) at B2 or any subsequent biopsy. The primary outcome analyzed was grade rate of grade reclassification, occurring at/or after B2 in patients who experienced antecedent tumor volume reclassification and chose to continue with AS. Volume reclassification (or an increase in tumor volume) was defined as more than 3 positive cores, or a single core with 50% or greater involvement (threshold volume for AS eligibility). Pathological grade reclassification was defined as GS greater than 3+3. Grade and volume reclassification was defined as both having occurred (GS 7 or greater, and greater than 50% single core involvement, or more than 3 positive cores).

Transrectal ultrasound guided prostate biopsies were taken according to standard practices using an end fire probe (C9-5 ICT, Philips, Bothell, Washington) with the patient under local anesthesia. Three genitourinary radiologists performed transrectal ultrasound guided prostate biopsies with a single operator performing 75% of them. Biopsy cores were collected and labeled by region sampled. Cancer location was captured systematically and entered into the database along with the percent involvement of each core. The number of positive cores was also entered with other clinical pathological variables. For B1 a template (10 to 12 cores) was used. For subsequent repeat biopsies an AS protocol template of 13 to 17 cores modeled on Babaian et al[20] was applied.[8,21] Some diagnostic biopsies (B1) were performed elsewhere. However, all followup biopsies were performed in-house. The study end point was grade reclassification, whether grade only or grade plus volume at the event biopsy. Medical charts of patients who demonstrated volume reclassification were reviewed.

For analysis men were censored if they demonstrated reclassification, elected to have treatment without reclassification or were lost to followup. Descriptive statistics used means with SD or medians with IQR. Comparisons were done using the ANOVA for continuous variables, and the chi-square and Fisher exact tests for categorical variables. All statistical tests were 2-sided with $p < 0.05$ considered statistically significant. SAS® statistical software version 9.1 was used for all analyses.