Outcomes of Scheduled vs For-Cause Biopsy Regimens for Prostate Cancer Active Surveillance

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Purpose: Active surveillance is a first line treatment option for patients with low risk prostate cancer but standardized regimens are lacking, including uniform protocols for surveillance prostate biopsy. We compared the outcomes of 2 active surveillance regimens that differ in whether a scheduled biopsy was performed in the absence of clinical progression.

Materials and Methods: We retrospectively reviewed the records of 313 consecutive patients with prostate cancer at a NCCN® (National Comprehensive Cancer Network®) institution who were assigned prospectively to 1 of 2 active surveillance biopsy regimens. A total of 149 patients underwent biopsy only for clinical concern (for-cause only) while 164 underwent for-cause biopsy plus scheduled annual or biannual biopsy. Times to biopsy, clinical progression, pathological reclassification and treatment were compared using Kaplan-Meier methodology.

Results: The for-cause only and scheduled plus for-cause biopsy groups were similar in NCCN risk category at active surveillance initiation. Median followup was 48 and 38 months, respectively. No significant difference was observed in prostate specific antigen dynamics or clinical progression rates. However, patients in the scheduled plus for-cause group underwent significantly more frequent biopsies ($p < 0.001$) and experienced more biopsy related complications ($p = 0.04$), pathological reclassification ($p = 0.02$) and treatment conversion ($p = 0.001$). Adverse prostatectomy pathology (pT3 or greater and/or Gleason primary pattern 4) and early metastasis events were rare in both groups.

Conclusions: Omitting a scheduled biopsy during active surveillance is associated with a decreased biopsy burden and treatment conversion. Although no increase in adverse pathology or early metastasis was observed in this study, longer followup in larger cohorts is necessary to determine the impact of scheduled biopsy omission on these adverse outcomes.

Key Words: prostatic neoplasms, biopsy, prostate-specific antigen, watchful waiting, complications

Abbreviations and Acronyms

AS = active surveillance
CaP = prostate cancer
FCO = for-cause only
PSA = prostate specific antigen
RPCI = Roswell Park Cancer Institute
S+FC = scheduled and for-cause

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ACTIVE surveillance for men with low grade, organ confined CaP avoids or delays long-term morbidity associated with radiation or radical prostatectomy. NCCN recommends AS as an option for patients at low risk with CaP and the preferred management choice in patients at very low risk with life expectancy less than 20 years.[1] Approximately half of

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contemporary patients with CaP diagnoses in the United States are candidates for AS[2] with AS selection by patients increasing nationally and internationally.[3,4] Reports of long-term oncologic outcomes of AS are scarce but many series with intermediate followup support the oncologic safety.[5–8]

The growing practice of AS contrasts with a paucity of scientific data describing optimal AS regimens. Standard AS practice includes 6-month PSA monitoring and 6 to 12-month prostate examinations, in addition to prostate biopsy triggered by a concerning change in clinical parameters (for-cause biopsy).[1] Most AS regimens also include scheduled surveillance biopsies (eg annual, biannual or irregular) for various durations to screen for pathological progression in the absence of clinical progression. Several studies have shown that normal PSA dynamics cannot reliably rule out adverse pathological reclassification on repeat biopsy.[1,6,9–13] While scheduled AS biopsy often leads to treatment conversion, the effect on oncologic outcomes remains unclear.

We investigated the association between scheduled biopsy and outcomes in patients on AS at a single NCCN institution. The focus was on biopsy burden, biopsy grade reclassification, treatment conversion and adverse surgical pathology. This study takes advantage of the fact that approximately half of all patients on AS in the last 2 decades at RPCI have been monitored prospectively by FCO biopsy while the remainder have been monitored prospectively by combination S+FC biopsy. This provided a unique opportunity to compare these 2 approaches.

MATERIALS AND METHODS

AS Regimens

This study was approved by the RPCI institutional review board. A prospectively maintained database of patients with CaP undergoing AS at RPCI was queried to identify all who began AS between January 1995 and June 2013. AS was offered to all men with low or very low risk CaP per NCCN guidelines,[14] in addition to select men with favorable intermediate risk CaP. All men were assigned prospectively to one of 2 biopsy regimens at AS initiation according to surgeon preference with all patients of any given surgeon assigned to the same regimen.

The FCO group was monitored by intent for biopsy based on clinical concern alone. The S+FC group was monitored by intent for scheduled biopsy (annually or biannually), in addition to for-cause biopsy. All men had age and health adjusted life expectancy greater than 10 years at AS initiation as determined using the United States Social Security indexes/calculator (https://www.ssa.gov/oact/population/longevity.html). The life expectancy of a man in the upper or lower quartile of health for his age was adjusted by a 50% increase or decrease, respectively. All patients on AS were monitored by 6-month serum PSA measurements and 6 to 12-month prostate examinations.[14]

Risk Classification and Progression

NCCN risk group at AS initiation was assigned to each patient based on NCCN guideline criteria.[14] Progression in NCCN risk during AS was defined as an increase in risk from low to intermediate, low to high or intermediate to high. Progression in biopsy grade during AS was defined as any adverse grade reclassification, which included an increase in total Gleason score or primary Gleason pattern. Progression in clinical risk group without regard to biopsy pathology was defined as a risk increase from low to intermediate, low to high or intermediate to high using NCCN risk parameters for cT stage and PSA only. Complications within 90 days of biopsy were graded using the Clavien system. Curative treatment was recommended based on biopsy grade progression, clinical progression or patient preference/anxiety.

Statistics

Patient characteristics in the FCO or S+FC group are reported using the median and IQR or mean and SD for continuous variables, and frequencies and relative frequencies for categorical variables. Comparisons were made between the FCO and S+FC groups with the 2-sample t-test or the Wilcoxon rank sum test as appropriate for continuous variables and the Fisher exact test for categorical variables. Time to event outcomes were summarized by group using the Kaplan-Meier methodology. Time to event comparisons between the FCO and S+FC groups were made using the log-rank test. Patients converted to treatment or watchful waiting/observation were censored from time to biopsy analyses at the time of conversion. All analysis was done in SAS®, version 9.4 with significance considered at $p < 0.05$.

RESULTS

Patient Baseline Features

A total of 313 AS patients were identified, including 149 (48%) monitored with intent for FCO biopsy and 164 (52%) monitored with intent for S+FC biopsy (supplementary table 1, http://jurology.com/). The 2 groups were similar at AS initiation with respect to age, Charlson score, PSA, clinical stage and NCCN risk category with approximately 90% of patients in each group at low risk (supplementary table 1, http://jurology.com/). The FCO cohort included significantly more Gleason 3 + 4 = 7 cancers at AS initiation than the S+FC group and the cancers tended to have a higher volume (supplementary table 1, http://jurology.com/). Confirmatory prostate biopsies prior to AS initiation were rare at 3% of each group.

Clinical Progression

Median followup during AS was 48 months (range 7 to 213) in patients in the FCO group and 38 months