# Impact of 5α-Reductase Inhibitors on Disease Reclassification among Men on Active Surveillance for Localized Prostate Cancer with Favorable Features

Charles Dai, Vishnu Ganesan, Joseph Zabell, Yaw A. Nyame, Nima Almassi, Daniel J. Greene, Daniel Hettel, Chad Reichard, Samuel C. Haywood, Hans Arora, Anna Zampini, Alice Crane, Jianbo Li, Ahmed Elshafei,* Cristina Magi-Galluzzi, Robert J. Stein, Khaled Fareed, Michael Gong, J. Stephen Jones,† Eric A. Klein and Andrew J. Stephenson‡

*From the Lerner College of Medicine (CD, VG, YAN, NA, DJG, DH, RJS, KF, MG, JSJ, EAK, AJS), Department of Urology, Glickman Urological and Kidney Institute (JZ, YAN, NA, DJG, CR, SCH, HA, AZ, AC, AE, RJS, KF, MG, JSJ, EAK, AJS), Quantitative Health Services (JL) and Robert J. Tomsich Pathology and Laboratory Medicine Institute (CM-G), Cleveland Clinic, Cleveland, Ohio, and Urology Department, Al Kasr Al Aini Hospital, Cairo University (AE), Cairo, Egypt*

**Purpose:** We determined the effect of 5α-reductase inhibitors on disease reclassification in men with prostate cancer optimally selected for active surveillance.

**Materials and Methods:** In this retrospective review we identified 635 patients on active surveillance between 2002 and 2015. Patients with favorable cancer features on repeat biopsy, defined as absent Gleason upgrading, were included in the cohort. Patients were stratified by those who did or did not receive finasteride or dutasteride within 1 year of diagnosis. The primary end point was grade reclassification, defined as any increase in Gleason score or predominant Gleason pattern on subsequent biopsy. This was assessed by multivariable Cox proportional hazards regression analysis.

**Results:** At diagnosis 371 patients met study inclusion criteria, of whom 70 (19%) were started on 5α-reductase inhibitors within 12 months. Median time on active surveillance was 53 vs 35 months in men on vs not on 5α-reductase inhibitors ($p < 0.01$). Men on 5α-reductase inhibitors received them for a median of 23 months (IQR 6–37). On actuarial analysis there was no significant difference in grade reclassification for 5α-reductase inhibitor use in patients overall or in the very low/low risk subset. The overall percent of patients who experienced grade reclassification was similar at 13% vs 14% ($p = 0.75$). After adjusting for baseline clinicopathological features 5α-reductase inhibitors were not significantly associated with grade reclassification (HR 0.80, 95% CI 0.31–1.80, $p = 0.62$).

**Abbreviations and Acronyms**

5-ARI = 5α-reductase inhibitor
AS = active surveillance
DRE = digital rectal examination
PSA = prostate specific antigen
REDEEM = Reduction with Dutasteride of Clinical Progression Events in Expectant Management Trial

Accepted for publication August 2, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

* Financial interest and/or other relationship with Endocare.

† Financial interest and/or other relationship with Cook.

‡ Correspondence: Glickman Urological and Kidney Institute, Cleveland Clinic, 9500 Euclid Ave., Q10, Cleveland, Ohio 44195 (telephone: 216-445-1062; FAX: 216-636-4492; e-mail: STEPHEA2@ccf.org).

**Editor's Note: This article is the second of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 578 and 579.**

0022-5347/18/1992-0445/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2017.08.006
Vol. 199, 445-452, February 2018
Printed in U.S.A.

Furthermore, no difference in adverse features on radical prostatectomy specimens was observed in treated patients ($p = 0.36$).

**Conclusions:** Among our cohort of men on active surveillance 5α-reductase inhibitor use was not associated with a significant difference in grade reclassification with time.

**Key Words:** prostatic neoplasms, watchful waiting, 5-alpha reductase inhibitors, neoplasm grading, risk factors

ACTIVE surveillance is an increasingly accepted treatment strategy in men with localized prostate cancer without adverse features.[1] Previously 5-ARIs have been studied as potential chemopreventive agents for prostate cancer.[2,3] The 5-ARIs finasteride and dutasteride primarily act by inhibiting prostatic conversion of serum testosterone to dihydrotestosterone, thereby disrupting androgen receptor signaling.[4]

The use of 5-ARIs in AS was specifically investigated in REDEEM, a placebo controlled, randomized trial in which dutasteride was used to prevent prostate cancer progression in men on AS.[5] At 3 years a statistically significant decrease in progression, defined as a change in grade or disease volume, or advancement to treatment for any reason, was observed which favored dutasteride compared to placebo. Overall positive results from REDEEM suggested that 5-ARIs may offer some clinical benefit in patients on AS. However, approximately 20% to 30% of scored events involved treatment in the absence of pathological triggers and there was a potential source of confounding due to the notable effect of 5-ARIs on serum PSA levels, which were not blinded in the trial.[6–8] Furthermore, true biological progression has the potential to be misrepresented by biopsy misclassification, especially in the immediate interim following diagnosis and in the absence of a confirmatory biopsy.[9]

Thus, we evaluated our institutional outcomes in men on 5-ARIs who pursued AS after undergoing repeat biopsy confirming favorable cancer features, which we defined as absent Gleason upgrading. Thus, the primary objective of this study was to assess whether 5-ARIs decrease grade reclassification in men with prostate cancer who were optimally selected by repeat biopsy for AS.

## MATERIALS AND METHODS

### Patient Population

After receiving institutional review board approval we retrospectively identified all men treated with AS from 2002 to 2015 at a large tertiary care academic institution. The composition, management and overall outcomes of this cohort have been previously described.[10] Briefly, the selection of patients on AS at our institution is assessed by a treating physician based on clinical characteristics (age, medical comorbidities and favorable disease features) as well as shared decision making. Surveillance includes periodic clinic visits every 6 to 12 months involving routine DRE and PSA measurements, repeat biopsy generally within 12 months of initial diagnostic biopsy and serial surveillance biopsies with a minimum of 12 cores generally every 1 to 2 years with rising PSA, abnormal magnetic resonance imaging and/or abnormal DRE as a consistent trigger for earlier biopsy.

### Clinicopathological and Demographic Data

Patient demographic and clinical information were obtained on age, race, date of diagnosis and time of definitive treatment if received, PSA measurements, prostate volume on transrectal ultrasound, DRE findings and date of last known followup. Biopsy data were also obtained from pathology reports, including the date of biopsy, total number of cores sampled and pathological findings such as Gleason score and number of positive cores. If a patient underwent radical prostatectomy, we reviewed surgical specimen pathology for adverse pathological features, including high grade disease (dominant pattern 4 or greater), extraprostatic extension, seminal vesicle invasion, positive margins or lymph node invasion using 2005 ISUP (International Society of Urological Pathology) criteria. All prostate biopsies and radical prostatectomy specimens were reviewed by our institutional genitourinary pathology team, who were blinded to treatment. Start to end dates for the 5-ARI prescription were extracted from the electronic medical records.

### Inclusion and Exclusion Criteria

The initial patient population primarily consisted of patients with NCCN® (National Comprehensive Cancer Network®) very low, low and select favorable intermediate risk prostate cancer. Only patients who underwent repeat biopsy after diagnosis confirming favorable cancer features, which we defined as absent Gleason upgrading, were included in the final study cohort. This approach was based on the rationale that any biological effect from exposure to 5-ARIs would not be adequately assessed in cases that were immediately upgraded upon repeat biopsy due to initial misclassification.

All repeat biopsy diagnoses were confirmed by genitourinary pathologists at our institution. Patients were categorized into 2 groups, including 1) those in whom 5-ARIs were initiated within 12 months after diagnosis and 2) 5-ARI treatment naïve patients. All 90 men who