Untreated Gleason Grade Progression on Serial Biopsies during Prostate Cancer Active Surveillance: Clinical Course and Pathological Outcomes

A. A. Hussein,* C. J. Welty,* N. Ameli,* J. E. Cowan,† M. Leapman,* S. P. Porten,* K. Shinohara* and P. R. Carroll‡,§

From the Department of Urology and UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California (AAH, CJW, NA, JEC, ML, SPP, KS, PRC), and Department of Urology, Cairo University, Cairo, Egypt (AAH)

Purpose: We describe the outcomes of patients with low risk localized prostate cancer who were upgraded on a surveillance biopsy while on active surveillance and evaluated whether delayed treatment was associated with adverse outcome.

Materials and Methods: We included men in the study with lower risk disease managed initially with active surveillance and upgraded to Gleason score 3+4 or greater. Patient demographics and disease characteristics were compared. Kaplan-Meier curve was used to estimate the treatment-free probability stratified by initial upgrade (3+4 vs 4+3 or greater), Cox regression analysis was used to examine factors associated with treatment and multivariate logistic regression analysis was used to evaluate the factors associated with adverse outcome at surgery.

Results: The final cohort comprised 219 men, with 150 (68%) upgraded to 3+4 and 69 (32%) to 4+3 or greater. Median time to upgrade was 23 months (IQR 11–49). A total of 163 men (74%) sought treatment, the majority (69%) with radical prostatectomy. The treatment-free survival rate at 5 years was 22% for 3+4 and 10% for 4+3 or greater upgrade. Upgrade to 4+3 or greater, higher prostate specific antigen density at diagnosis and shorter time to initial upgrade were associated with treatment. At surgical pathology 34% of cancers were downgraded while 6% were upgraded. Cancer volume at initial upgrade was associated with adverse pathological outcome at surgery (OR 3.33, 95% CI 1.19–9.29, p=0.02).

Conclusions: After Gleason score upgrade most patients elected treatment with radical prostatectomy. Among men who deferred definitive intervention, few experienced additional upgrading. At radical prostatectomy only 6% of cases were upgraded further and only tumor volume at initial upgrade was significantly associated with adverse pathological outcome.

Key Words: watchful waiting, neoplasm grading, disease progression, prostatic neoplasms

Abbreviations and Acronyms

AS = active surveillance
BXn = biopsy number after initial upgrade
GS = Gleason score
PCa = prostate cancer
PSA = prostate specific antigen
PSAD = PSA density
PSM = positive surgical margins
RP = radical prostatectomy

Accepted for publication January 15, 2015.

Study received institutional review board approval.

Supported by the U.S. Department of Defense Prostate Cancer Research Program (W81XWH-13-2-0074 and W81XWH-11-1-0489).

* Nothing to disclose.

† Financial interest and/or other relationship with Abbott Labs.

‡ Correspondence: Department of Urology, University of California, San Francisco, 1600 Divisadero St., Box 1695, San Francisco, California 94143-1695 (telephone: 415-353-7098; FAX: 415-353-9932; e-mail: pcarroll@urology.ucsf.edu).

§ Financial interest and/or other relationship with NIH, Department of Defense, Myriad Genetics, AUA Update, Genomic Health and Medivation/Astellas.

See Editorial on page 8.

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 268 and 269.

In the contemporary PSA era the widespread use of PSA screening has contributed to an estimated reduction in prostate cancer mortality of 20% to 50%.[1,2] However, this has been at the expense of over diagnosis and subsequent overtreatment of cancers that may not have posed a significant threat to patients. Currently, although the American Urological Association and

0022-5347/15/1941-0085/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.01.077
Vol. 194, 85-90, July 2015
Printed in U.S.A.

National Comprehensive Cancer Network recommendations have been designed to limit over detection, neither prevent it.[3,4]

The long natural history of PCa and detection of potentially indolent tumors have led to the development of active surveillance as an initial management strategy. AS for low risk disease allows postponing or avoiding the possible morbidities and adverse quality of life consequences that may be associated with treatment. Disease progression is actively monitored while maintaining an opportunity for cure. With time, more than a third of patients will be reclassified as at higher risk and pursue treatment.[5,6] In most cases reclassification to higher risk is due to upgrading at repeat biopsy.[7] Most cohorts use grade progression to Gleason scores 3+4 or higher as a trigger for intervention and grade progression on serial biopsy is strongly associated with time to treatment.[8]

It remains unclear which parameters, including grade progression, truly identify patients who need immediate, active treatment. Although most recommend active treatment in case of progression on repeat biopsies, some patients elect to continue on AS. In this context we describe the characteristics, followup and outcomes of patients who continued on AS in spite of grade progression on surveillance biopsy or sought treatment.

PATIENTS AND METHODS

Study Cohort

This was a retrospective observational study of patients from the University of California at San Francisco Urologic Oncology Database conducted under institutional review board approval. We included consented men followed for at least 6 months after diagnosis with lower risk localized PCa (GS 3+3 or lower at diagnosis and clinical T1 or T2 tumor) who were initially managed with AS. Additional inclusion criteria were a minimum of 6 cores taken at diagnostic biopsy, 33% or less positive and single core positivity 50% or less. We further restricted the analysis to include patients who further upgraded to GS 3+4 or greater while on AS (fig. 1).

AS Protocol

The recommended AS regimen at our institution consisted of digital rectal examination, PSA testing at 3-month intervals and transrectal ultrasound guided prostate biopsies generally performed at 12 to 24-month intervals. Repeat biopsies included at least 14 cores taken from all sextants and included anterior gland sampling. Intervention was offered to men who experienced significant clinical or biopsy progression beyond the inclusion criteria.

Statistical Analysis

Patient demographics and disease characteristics were compared using means, medians and contingency tables with p values based on t-statistics, Wilcoxon signed rank test and chi-squared tests. Treatment after initial upgrade and adverse outcome (defined as having stage pT3a or greater and/or positive lymph nodes) among the subset of patients who underwent RP were used as the response variables. As PSM may be surgeon and technique dependent, a separate model for PSM as an adverse outcome was performed. We defined initial upgrade on any surveillance biopsy as an increase from GS 3+3 or lower at diagnosis to 3+4 or greater. We then categorized men with initial upgrade into 2 groups: 3+4 and 4+3 or greater. The first biopsy after initial upgrade was referred to as BX1, the second biopsy after initial upgrade as BX2, and so forth. The initial upgrade was used as the primary independent variable. Other covariates included in the model were age, PSAD, prostate volume and CAPRA (Cancer of the Prostate Risk Assessment) score risk classification at diagnosis, PSA before last biopsy or RP, time from diagnosis to initial upgrade, time from initial upgrade to RP and cancer volume (percentage of positive total cores and maximum of a single core positive) at initial upgrade. We also examined subsequent GS changes when compared to the initial upgrade defined as a further upgrade, downgrade, no change or benign. Biochemical failure was defined as achieving a PSA of 0.2 ng/ml or greater on 2 consecutive post-RP tests.

We used Kaplan-Meier curves to estimate the probability of being treatment-free stratified by initial upgrade groups 3+4 and 4+3 or greater, and the log rank test to determine whether the difference between the 2 groups was statistically significant. Time was censored if the treatment event had not been observed for an individual. Cox proportional hazard regression analysis was used to examine factors associated with treatment. Multivariate logistic regression analysis was used to evaluate the effect of covariates on the probability of having adverse outcome at RP. Statistical analyses were performed using SAS® software version 9.3.

RESULTS

A total of 525 men met the initial inclusion criteria. Mean age at diagnosis was 61.6 years (range 42 to 82) with median PSA 5.2 ng/ml (IQR 4.0–7.2). Most men were diagnosed with clinical stage T1 (70%) and low CAPRA score (91%). Median followup after diagnosis was 59 months (IQR 37–89). The final cohort for analysis comprised 219 (42%) men who experienced a GS upgrade on followup biopsy, of whom 150 (68%) were upgraded to 3+4 and 69 (32%) upgraded to 4+3 or greater. There were 26 men who had no subsequent biopsy or treatment at time of analysis (17 with pattern 3+4 and 9 with 4+3 or greater). Of these, 17 were followed with PSA and/or ultrasound and the remaining 9 did not have a followup visit after upgrading. Median time to the initial upgrade was 23 months (IQR 11–49). Demographics and tumor characteristics are shown in the supplementary table (http://jurology.com/).

Among 133 men who had an initial upgrade to 3+4, 43% (57) stayed on AS and underwent BX1. On