Incidence and Predictors of Upgrading and Up Staging among 10,000 Contemporary Patients with Low Risk Prostate Cancer

Kathryn T. Dinh, Brandon A. Mahal, David R. Ziehr, Vinayak Muralidhar, Yu-Wei Chen, Vidya B. Viswanathan, Michelle D. Nezolosky, Clair J. Beard, Toni K. Choueiri, Neil E. Martin, Peter F. Orio, Christopher J. Sweeney, Quoc D. Trinh* and Paul L. Nguyen†,‡

From Harvard Medical School (KTD, BAM, DRZ, VM), Harvard T.H. Chan School of Public Health (YWC), Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital (VBV, MDN), Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School (CJB, NEM, PFO, PLN), Department of Medical Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School (TKC, CJS), and Division of Urology, Brigham and Women's Hospital, Harvard Medical School (QDT), Boston, Massachusetts

Purpose: We determined the incidence of pathological upgrading and up staging for contemporary, clinically low risk patients, and identified predictors of having occult, advanced disease to inform the selection of patients for active surveillance.

Materials and Methods: We studied 10,273 patients in the SEER database diagnosed with clinically low risk disease (cT1c/T2a, prostate specific antigen less than 10 ng/ml, Gleason 3+3=6) in 2010 to 2011 and treated with prostatectomy. The primary outcome was the incidence of upgrading to pathological Gleason score 7-10 or up staging to pathological T3-T4/N1 disease. Multivariable logistic regression of cases with complete biopsy data (5,581) identified significant predictors of upgrading or up staging, which were then used to create a risk stratification table.

Results: At prostatectomy 44% of cases were upgraded and 9.7% were up staged. Multivariable analysis of 5,581 patients showed age, prostate specific antigen and percent positive cores (all $p < 0.001$) but not race were associated with occult, advanced disease. With these variables dichotomized at the median, age older than 60 years (AOR 1.39), prostate specific antigen greater than 5.0 ng/ml (AOR 1.28) and more than 25% positive cores (AOR 1.76) were significantly associated with upgrading (all $p < 0.001$). Similarly, age older than 60 years (AOR 1.42), prostate specific antigen greater than 5.0 ng/ml (AOR 1.44) and more than 25% positive cores (AOR 2.26) were associated with up staging (all $p < 0.001$). Overall 60% of 5,581 low risk cases with prostate specific antigen 7.5 to 9.9 ng/ml and more than 25% positive cores were upgraded. This study is limited by possible bias introduced by only using patients selected for prostatectomy.

Conclusions: Nearly half of clinically low risk patients harbor Gleason 7 or greater, or pT3 or greater disease, and should be risk stratified by prostate specific antigen and percent positive cores for consideration of further testing before deciding on active surveillance.

Key Words: neoplasm grading, neoplasm staging, prostatic neoplasms, SEER program, watchful waiting

Abbreviations and Acronyms

AOR = adjusted odds ratio

AS = active surveillance

MRI = magnetic resonance imaging

MVA = multivariable logistic regression analysis

PCa = prostate cancer

PPC = percent positive cores

PSA = prostate specific antigen

SEER = Surveillance, Epidemiology, and End Results

Accepted for publication February 4, 2015.

Supported by Fitz's Cancer Warriors, David and Cynthia Chapin, the Prostate Cancer Foundation, Hugh Simons in honor of Frank and Anne Simons, Scott Forbes and Gina Ventre, and a grant from an anonymous family foundation.

This project was done under protocol #12-513 approved by the institutional review board of Brigham and Women's Hospital and Dana Farber Cancer Institute.

* Financial interest and/or other relationship with Intuitive Surgical.

† Correspondence: Telephone: 617-732-7936; FAX: 617-975-0912; e-mail: pnguyen@LROC.harvard.edu).

‡ Financial interest and/or other relationship with Medivation and Genome Dx.

0022-5347/15/1942-0343/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.02.015
Vol. 194, 343-349, August 2015
Printed in U.S.A.

In 2014 an estimated 233,000 men were diagnosed with prostate cancer in the United States and most of these men were diagnosed with low risk PCa.[1] Due to the concern that clinically low risk PCa may often be overtreated, there is increased interest in active surveillance to reduce unnecessary treatment for these patients.[2–5] However, reviews of AS selection criteria have demonstrated that current practice is not sensitive or specific for insignificant disease,[6,7] defined as Gleason 6 or less and organ confined disease. Criteria for AS could be improved by identifying certain diagnostic features that place clinically low risk men at increased risk for harboring occult Gleason 7-10 or T3-T4 disease. Past studies have shown a disparity between biopsy Gleason score and clinical stage with prostatectomy Gleason score and stage.[8–16] However, many included all risk groups, limiting their application to current AS eligible patients. Further work is necessary to understand the incidence of upgrading and up staging among contemporary, low risk patients, and how to identify those at risk for occult, more advanced disease.

The purpose of this present study is twofold. 1) We used the SEER database,[17] including newly available data on biopsy and pathological Gleason sum and score, clinical T stage, and pathological T stage, to estimate the prevalence of upgrading and up staging among contemporary low risk PCa cases diagnosed in 2010 to 2011 and treated with prostatectomy. 2) We used a multivariable logistic analysis to identify features associated with an increased risk of harboring more advanced disease. These factors may help identify patients with low risk PCa with concerning features who should have further evaluation before AS, such as advanced imaging or additional MRI guided biopsies.

PATIENTS AND METHODS

Patient Population

SEER is a population based cancer registry, sponsored by the U.S. National Cancer Institute, that collects demographic characteristics, and cancer incidence, treatment and survival data for approximately 28% of the U.S. population.[17] We identified men in SEER diagnosed in 2010 to 2011 with low risk, histologically confirmed prostate adenocarcinoma primarily treated with prostatectomy. Low risk PCa was defined as pretreatment PSA less than 10.0 ng/ml, biopsy Gleason 3+3 and clinical T1c-T2a. The study included only 2010 to 2011 to use new, PCa specific variables in SEER, including total number of biopsy cores and number of positive cores. We used SEER*Stat 8.1.5 to access data.

Our initial cohort was 10,478 men, excluding those diagnosed at autopsy or by death certificate, whose pathological data was from autopsy and those who received neoadjuvant chemoradiation. Patients with incomplete data for biopsy Gleason sum, clinical T stage, pathological Gleason sum or pathological T stage were also excluded from study (205). Our final cohort was 10,273 patients, of whom 5,581 had complete data for the number of biopsy and positive cores.

Demographic data included age at diagnosis, race and marital status. Clinical data included pretreatment PSA, biopsy Gleason score and sum, clinical T stage, number of biopsy cores and number of cores positive for PCa. The percent positive cores was defined as the number of positive cores divided by the total number of cores biopsied. Pathological data included prostatectomy Gleason score and sum, TN stage, and tumor size (mm). Tumor size was available for 3,615 patients.

Statistical Analysis

Demographic, clinical and pathological characteristics of our sample were described. Upgrading was defined as pathological Gleason 7-10 and up staging as pathological T3-T4/N0-1. We further stratified Gleason 3+4 vs 4+3 or greater and pT3a vs pT3b-4/N0-1 to define aggressive, locally advanced disease. Our primary outcome was the proportion of cases upgraded or up staged at prostatectomy. We also calculated the rate of adverse tumor size, defined as tumors larger than 20 mm.

Our second outcome was to identify demographic and clinical characteristics associated with upgrading or up staging by MVA using the subset of patients with complete biopsy data (5,581). Age, PSA and PPC were treated as continuous variables in our initial models. Race was defined as black or nonblack and marital status as married or not married.

In a secondary MVA (5,581) all variables were binary. Age and PSA were dichotomized near the median, with age 60 or younger vs older than 60, PSA 5.0 ng/ml or less vs greater than 5.0, and PPC 25% or less vs greater than 25%. Finally, we used 2 factors associated with upgrading and up staging to create a stratified risk table. All p values reported were 2-sided with significance at $p < 0.05$. We used STATA® (version 11.1) for statistical analysis. The institutional review board at the study institution approved this study and a waiver for informed consent was obtained.

RESULTS

Baseline Patient Characteristics

Tables 1 and 2 list baseline demographic, clinical and pathological characteristics for the total cohort. Median age was 60 years (range 34 to 92). Most patients were married (77.7%) and white (83.8%), and there were 1,215 African-American patients (11.8%). Median PSA was 5.0 ng/ml (range 0.1 to 9.9) and 92.7% of cases were cT1c vs 7.3% cT2a. Median tumor size was 13 mm (IQR 7–18).

Incidence of Upgrading and Up Staging

Of the patients in our cohort 44% (4,467) had disease upgraded to Gleason 7-10 (fig. 1). Of these patients 86.2% (3,842) had 3+4=7 disease, 10.6% (473) had 4+3=7 disease and 1.3% (137) had Gleason 8-10