Original Study

Pathologic Outcomes of Gleason 6 Favorable Intermediate-Risk Prostate Cancer Treated With Radical Prostatectomy: Implications for Active Surveillance

David D. Yang,[1] Brandon A. Mahal,[2] Vinayak Muralidhar,[2] Marie E. Vastola,[3] Ninjin Boldbaatar,[3] Shelby A. Labe,[3] Michelle D. Nezolosky,[3] Peter F. Orio, III,[1,3] Martin T. King,[1,3] Neil E. Martin,[1,3] Kent W. Mouw,[1,3] Quoc-Dien Trinh,[1,4] Paul L. Nguyen[1,3]

Abstract

We examined the pathologic outcomes of 2807 men with Gleason 6 favorable intermediate-risk (FIR) prostate cancer treated with radical prostatectomy; 25.5% of patients with prostate-specific antigen of 10 to 20 ng/mL and 12.4% with cT2b to T2c stage harbored higher grade or stage disease, suggesting that Gleason 6 FIR patients with cT2b to T2c tumors might generally be reasonable candidates for active surveillance.

Background: The safety of active surveillance (AS) for Gleason 6 favorable intermediate-risk (FIR) prostate cancer is unknown. To provide guidance, we examined the incidence and predictors of upgrading or upstaging for Gleason 6 FIR patients treated with radical prostatectomy. **Patients and Methods:** We identified 2807 men in the National Cancer Database diagnosed from 2010 to 2012 with Gleason 6 FIR disease (<50% positive biopsy cores [PBC] with either prostate-specific antigen [PSA] of 10-20 ng/mL or cT2b-T2c disease) treated with radical prostatectomy. Logistic regression was used to identify predictors of upgrading (Gleason 3+4 with tertiary Gleason 5 or Gleason ≥4+3) or upstaging (pT3-4/N1). **Results:** Fifty-seven percent of the cohort had PSA of 10 to 20 ng/mL; 25.5% patients with PSA of 10 to 20 ng/mL and 12.4% with cT2b to T2c disease were upgraded or upstaged. In multivariable analysis, predictors of upgrading or upstaging included increasing age ($P = .026$), PSA ($P = .001$), and percent PBC ($P < .001$), and black race versus white ($P = .035$) for patients with PSA of 10 to 20 ng/mL and increasing PSA ($P = .001$) and percent PBC ($P < .001$) for patients with cT2b to T2c disease. Men with PSA of 15.0 to 20.0 ng/mL or 37.5% to 49.9% PBC with PSA of 10 to 20 ng/mL had >30% risk of upgrading or upstaging, whereas cT2b to T2c patients with <12.5% PBC or PSA <5.0 ng/mL had <10% risk. **Conclusion:** We found that Gleason 6 FIR patients with cT2b to T2c tumors had a low risk of harboring higher grade or stage disease and would be reasonable AS candidates, whereas patients with PSA of 10 to 20 ng/mL had a high risk and might generally be poor AS candidates.

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Introduction

Active surveillance (AS) has emerged as the preferred initial management strategy for patients with low-risk prostate cancer to decrease the overtreatment of clinically indolent disease. Some patients with a Gleason score of 6 on biopsy have intermediate-risk disease based on the presence of other intermediate-risk features, and it is unknown whether AS can be safely extended to these patients. National Comprehensive Cancer Network guidelines state

[1]Harvard Medical School, Boston, MA
[2]Harvard Radiation Oncology Program, Boston, MA
[3]Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA
[4]Division of Urological Surgery and Center for Surgery and Public Health, Brigham and Women's Hospital, Boston, MA

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Address for correspondence: Paul L. Nguyen, MD, Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, 75 Francis St, Boston, MA 02115
Fax: 617-975-0912; e-mail contact: Paul_Nguyen@dfci.harvard.edu

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that AS may be considered an option for patients with favorable intermediate-risk (FIR) prostate cancer[1] (<50% positive biopsy cores [PBC] with 1 intermediate-risk factor, i.e., Gleason 3+4, cT2b-T2c stage, or prostate-specific antigen [PSA] of 10-20 ng/mL without high-risk features),[2] but prospective evidence on AS for Gleason 6 FIR disease is scarce because intermediate-risk patients are poorly represented in reported AS cohorts.[3-7] Retrospective series suggest that select intermediate-risk patients have favorable oncologic outcomes,[2] which might not be significantly worse than low-risk patients.[8] However, the presence of an intermediate-risk factor in a Gleason 6 tumor suggests the presence of occult higher grade or stage disease, which might cause significant harm if not definitively treated. This presence of occult aggressive disease likely explains why some patients with Gleason 6 disease at biopsy suffer metastases or die of prostate cancer.

To provide guidance on selecting Gleason 6 FIR patients for AS, we examined the incidence and predictors of upgrading to Gleason 3+4 with tertiary Gleason 5 or Gleason ≥4+3 (because of the relatively favorable prognosis of Gleason 3+4 without tertiary Gleason 5 disease)[2,8,9] and upstaging to pT3-4/N1 disease in a national cohort of Gleason 6 FIR patients who underwent radical prostatectomy (RP).

Patients and Methods

Data Source

The National Cancer Database (NCDB) is a hospital-based database that captures approximately 70% of newly diagnosed cancers in the United States.[10] It was created as a joint effort between the Commission on Cancer and the American Cancer Society.

Study Cohort

We identified 2807 men in the NCDB who were diagnosed from 2010 through 2012 with Gleason 6 FIR prostate cancer (<50% PBC and either cT2b-T2c or PSA of 10-20 ng/mL), did not have clinical evidence of nodal or metastatic disease, and were treated with RP. The first year that patients consistently had information on percent PBC was 2010, and 2012 was the most recent year available. Patients with incomplete sociodemographic (age, race, treatment facility type, insurance status, zip code-level income and education, and distance to treatment facility), clinical (Charlson-Deyo comorbidity score, PSA, number of biopsy cores examined, and percentage of PBC, and clinical T stage), or pathologic information (Gleason score at RP and pathologic T stage) were excluded. Because the 2014 International Society of Urological Pathology consensus conference modified the Gleason reporting system such that a Gleason 3+3 RP specimen with tertiary Gleason 4 disease on the basis of the 2005 consensus is now to be considered Gleason 3+4 disease,[11] we categorized the 84 patients with Gleason 3+3 with tertiary Gleason 4 disease at RP in our cohort to have Gleason 3+4 disease.

Statistical Analysis

The outcome of interest was the presence of upgrading, defined as Gleason 3+4 with tertiary Gleason 5 or Gleason ≥4+3 disease, or upstaging, defined as pT3-4 or pN1 disease at RP. We also presented data on surgical margin status but did not include it in the definition of upstaging because margin status is partially dependent on the surgeon's characteristics. We did not include patients with Gleason 3+4 without tertiary Gleason 5 disease as upgrading because of its relatively indolent course.[2,8,9] For instance, Raldow et al, using a prospective cohort of 5580 patients treated with brachytherapy, did not report a difference in prostate cancer-specific mortality between men with low-risk compared with FIR disease (adjusted hazard ratio, 1.64; 95% confidence interval [CI], 0.76-3.53; $P = .21$).[8] Furthermore, patients with Gleason 3+4, PSA <10 ng/mL, cT1 to T2a disease are also considered to be FIR and treated similarly to Gleason 6 FIR patients.[1,2] For Gleason 3+4 FIR patients, the presence of Gleason 3+4 without tertiary Gleason 5 on RP would not be considered upgrading. As such, we did not include Gleason 3+4 without tertiary Gleason 5 to be upgrading for Gleason 6 FIR patients.

Logistic regression was used to determine whether age, PSA, percent PBC, clinical T stage, and race were associated with upgrading or upstaging with additional adjustment for treatment facility type (community, comprehensive community, and academic/research).[10] To illustrate the incidence of upgrading or upstaging, PSA was divided into groups of 10.0 to 14.9 and 15.0 to 20.0 ng/mL for patients with PSA of 10 to 20 ng/mL and <5.0 and 5.0 to 9.9 ng/mL for patients with cT2b to T2c disease; percent PBC was categorized as <12.5%, 12.5% to 24.9%, 25.0% to 37.4%, and 37.5% to 49.9%; and age was divided into quartiles for the entire study cohort consisting of ≤55, 56 to 61, 62 to 65, and ≥66 years. Results were considered statistically significant if $P < .05$. Analyses were conducted using Stata/SE version 14.2 (StataCorp, College Station, TX). An institutional review board waiver was obtained before undertaking this study.

Results

Baseline Patient Characteristics

Baseline patient characteristics grouped according to PSA of 10 to 20 ng/mL or cT2b to T2c disease are listed in Table 1.

Incidence of Upgrading and Upstaging for Gleason 6 FIR Patients

Overall, 19.8% (557) of the study cohort was upgraded to Gleason 3+4 with tertiary Gleason 5 or Gleason ≥4+3 or upstaged to pT3-4 or pN1 at RP (Figure 1, Table 2). Of the cohort, 6.9% (193) were upgraded only, 8.6% (240) were upstaged only, and 4.4% (124) were upgraded and upstaged.

Incidence and Predictors of Upgrading and Upstaging for Gleason 6 FIR Patients With PSA of 10 to 20 ng/mL

Of Gleason 6 FIR patients with PSA of 10 to 20 ng/mL, 25.5% (408) were upgraded or upstaged at RP (Table 1). In multivariable analysis, increasing age (adjusted odds ratio [AOR], 1.02 per year; 95% CI, 1.00-1.04; $P = .026$), PSA (AOR, 1.08 per ng/mL; 95% CI, 1.03-1.12; $P = .001$), and percent PBC (AOR, 1.25 per 10%; 95% CI, 1.13-1.38; $P < .001$), as well as black race compared with white (AOR, 1.43; 95% CI, 1.03-1.98; $P = .035$) were significantly associated with upgrading or upstaging, whereas clinical T stage was not ($P = .715$; Table 3).

Figure 2 shows the incidence of upgrading or upstaging according to percent PBC (Figure 2A), PSA (Figure 2C), and age (Figure 2E).