The Presence of High-grade Prostatic Intraepithelial Neoplasia or Atypia on Prostate Biopsy Does Not Adversely Affect Prostatectomy Outcomes for Patients Otherwise Eligible for Active Surveillance

Eugene J. Pietzak III, Abdo E. Kabarriti, Phillip Mucksavage, Thomas Bavaria, Keith Van Arsdalen, S. Bruce Malkowicz, Alan J. Wein, and Thomas J. Guzzo

OBJECTIVE To investigate if the presence of concomitant high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) on biopsy increases the risk of occult adverse pathology in patients otherwise suitable for active surveillance (AS).

METHODS Patients with D'Amico low-risk prostate cancer on ≥10-core biopsy who underwent radical prostatectomy at our academic center were evaluated for eligibility for AS by either Epstein criteria or Memorial Sloan Kettering Cancer Center (MSKCC) criteria. Prostatectomy specimens of patients eligible for AS were compared to determine if the presence of clinical HGPIN or ASAP affected the primary outcomes of pathologic upstaging and Gleason score upgrading.

RESULTS Of 553 patients with low-risk prostate cancer, 400 patients (72.3%) met the MSKCC criteria, whereas only 170 patients (30.7%) met the Epstein criteria. HGPIN was present in approximately 32%, and ASAP in approximately 12%, of each AS cohort. On univariate and multivariate analyses, HGPIN and ASAP had no impact on the rate of upgrading and upstaging in either Epstein or MSKCC AS-eligible patients. Furthermore, the presence of HGPIN and ASAP had no impact on the 5-year biochemical recurrence-free survival.

CONCLUSION The presence of HGPIN or ASAP does not increase the risk of upgrading, upstaging, or adverse pathology at the time of prostatectomy for patients who meet the AS criteria. If otherwise suitable, HGPIN and ASAP should not impact the decision to choose AS. However, analysis of prospective AS trials is required to determine if HGPIN or ASAP impacts tumor progression once on AS. UROLOGY 84: 1442–1447, 2014. © 2014 Elsevier Inc.

In recent years, the diagnosis and treatment of prostate cancer (PCa) has been under increased scrutiny. Multiple criteria have been developed to help determine suitable candidates for active surveillance (AS) in an effort to better balance the risk of PCa morbidity and mortality with the adverse effects associated with treatment.[1] There are still no universally accepted optimal AS criteria. Although most criteria focus on the grade and volume of PCa found on biopsy, no AS criteria address other histologic findings, such as high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP).[2]

Although subject to debate, HGPIN is thought by some to be a precursor lesion of PCa due to similar genetic alterations. Although the association between unifocal HGPIN and PCa is less robust than initially believed, multifocal HGPIN does appear to increase the risk of detecting PCa on repeat biopsy compared with benign biopsies.[3,4] Furthermore, ASAP is diagnosed when a high suspicion for PCa exists but the definitive diagnosis of carcinoma cannot be established. Repeating prostate biopsies with additional samples taken in the area of the ASAP can identify PCa in >50% of patients.[3]

Given the association between both HGPIN and ASAP with PCa, an obvious question is whether these histologic findings on biopsy should be factored into the

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From the Division of Urology, Department of Surgery, Hospital of University of Pennsylvania, Philadelphia, PA

Address correspondence to: Eugene J. Pietzak III, M.D., Division of Urology, Department of Surgery, Hospital of University of Pennsylvania Philadelphia, PA 19104. E-mail: Eugene.pietzak@uphs.upenn.edu

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decision making process of AS vs definitive treatment. To the best of our knowledge, this question remains unanswered. To this aim, we looked at the impact of clinical HGPIN and clinical ASAP on prostatectomy outcomes for patients who are eligible for 2 commonly used AS criteria but elected for surgical treatment. We hypothesized that HGPIN would not be associated with an increased risk of Gleason score upgrading and pathologic upstaging for AS-eligible patients, but ASAP would be associated with these worse outcomes.

METHODS

We identified patients with D'Amico low-risk PCa (Gleason score [GS] ≤6, prostate-specific antigen [PSA] level ≤10 ng/mL, and clinical stage T1c-T2a) found on ≥10-core biopsy and treated with retropubic radical prostatectomy (RP) from 1998 to 2008 at a single academic center.[5] We then evaluated this cohort for eligibility by 2 AS criteria based on their biopsy characteristics. Patients who met either AS criteria were then analyzed for the presence or absence of clinical HGPIN, as well as the presence or absence of clinical ASAP.

Epstein criteria and Memorial Sloan Kettering Cancer Center (MSKCC) criteria were the 2 AS criteria selected for this study. Patients were considered to meet Epstein criteria if they had clinical stage T1c, GS ≤6, ≤50% carcinoma involvement of any core, ≤2 positive core, and PSA density ≤0.15 ng/mL.[6] Patients were considered to have met MSKCC criteria if they had clinical stage T1c-T2a, PSA level ≤10 ng/mL, GS ≤6, ≤3 positive core, and ≤50% involvement of any core.[7] Patients who were diagnosed with PCa on biopsies of <10 cores were excluded from this study.[8]

Comparisons were then made for those meeting AS criteria with clinical HGPIN against those meeting AS criteria without clinical HGPIN. Separate analyses were performed for those meeting Epstein criteria and those meeting MSKCC criteria. We then repeated this analysis looking at those meeting AS criteria with clinical ASAP against those meeting AS criteria without clinical ASAP. Again, separate analyses were performed for Epstein and MSKCC criteria.

For each comparison, the clinical characteristics and pathologic results were analyzed. The primary outcomes for this study were differences in the rate of upgrading and upstaging at the time of prostatectomy. Upgrading was defined as the presence of any disease within the prostatectomy specimen with GS ≥7, whereas upstaging was defined as disease with pathologic stage ≥pT3. Differences in biochemical recurrence (BCR) were also calculated for the groups. BCR was defined as 2 separate measurements of serum PSA level >0.2 ng/mL using chemiluminescent enzyme immunometric assay.

The processing and pathologic analysis of RP specimens at our institution has been previously described.[9] A dedicated genitourinary (GU) pathologist reviewed all biopsies and RP specimens, including the rereview of biopsies performed outside our institution. The GU pathologist determined the presence or absence of HGPIN, ASAP, and carcinoma in the specimens.

Statistical Analysis

Statistical analysis was performed using Stata 12.0 (College Station, TX). Continuous variables were reported as median values with interquartile rankings (IQR). The Shapiro-Wilk test was used to determine nonparametric distribution for continuous variables; therefore, the Wilcoxon rank sum test was used for comparisons. Categorical variables were analyzed using the chi-square test and the Fisher exact test when appropriate. The log-rank test was used to detect differences in BCR survival. Statistical significance was declared if $P \leq .05$. Multiple logistic regression analyses were performed for the primary outcomes in both Epstein and MSKCC cohorts using predictor variables with P values ≤.2 on univariate analysis and for variables thought to have a priori interactions (age, PSA, ASAP, and HGPIN).

RESULTS

Included in the entire study cohort were 553 consecutive patients with D'Amico low-risk PCa diagnosed on ≥10-core biopsy. The median time from biopsy to RP was 3.3 months (IQR, 2.7, 4.2) for the entire cohort.

Of the 553 patients in the study cohort, 168 (30.4%) had clinical HGPIN, whereas only 76 (13.7%) had clinical ASAP. Of the entire 553 patient cohort, 400 (72.3%) were eligible for MSKCC AS protocol, whereas only 170 (30.7%) were eligible by Epstein AS criteria. Of the 170 patients meeting Epstein criteria, 56 (32.9%) had clinical HGPIN and 20 (11.7%) had clinical ASAP. Of the 400 patients meeting MSKCC criteria, 124 (31.1%) had clinical HGPIN and 47 (11.8%) had clinical ASAP.

Comparison Number 1: Presence vs Absence of HGPIN in Epstein AS–eligible Patients

Comparing the clinical characteristics for Epstein AS–eligible patients, no clinical variable that was analyzed was statistically different as seen in Supplementary Table 1. Furthermore, no statistical difference was found on comparing RP specimens with regards to upgrading, upstaging, or adverse features (Table 1). Additionally, the presence of clinical HGPIN had no impact with regard to the risk of biochemical failure in Epstein-eligible patients ($P = .96$). Five-year BCR-free survival (BCRFS) was 100% for both groups.

Multivariate logistic regression modeling for Epstein-eligible patients is listed in Table 2. Only serum PSA level was a significant predictor of upgrading, and only the total number of biopsy cores taken was inversely related to the risk of upstaging. Clinical HGPIN was not a predictor of either upgrading or upstaging within the Epstein AS–eligible cohort.

Comparison Number 2: Presence vs Absence of HGPIN in MSKCC AS–eligible Patients

The results of the univariate analysis for clinical features between patients meeting MSKCC criteria with clinical HGPIN and those without HGPIN can be seen in Supplementary Table 1. Those diagnosed with HGPIN were more likely to have more biopsy cores taken (13.5 [IQR, 11-16] vs 12 [IQR, 11-14]; $P = .001$) and to have ≤2 cores involved with carcinoma (108 of 124 [89.3%] vs 218 of 275 [80%]; $P = .02$). MSKCC eligible patients with HGPIN were also more likely to have concomitant ASAP than MSKCC-eligible patients