Original Study

Prognostic Significance of the Disparity Between Biopsy and Pathologic Gleason Score After Radical Prostatectomy in Clinical Candidates for Active Surveillance According to the Royal Marsden Criteria

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Abstract

We identify the biochemical outcome according to biopsy Gleason score among patients who are clinical candidate for active surveillance. We found that different adverse pathologic outcomes and biochemical outcomes were shown according to biopsy pattern although the patients have the same pathologic GS 3+4 after RP.

Introduction: We identify the biochemical outcome according to biopsy Gleason score (bGS) among patients who are clinical candidate for active surveillance. We found that different adverse pathologic outcomes and biochemical outcomes were shown according to biopsy pattern although the patients have the same pathologic Gleason score (pGS) 3+4 after RP. **Background:** To identify the biochemical recurrence rate (BCR) according to a pGS upgrade after radical prostatectomy among men with prostate cancer who are clinical candidates for active surveillance (AS) according to the Royal Marsden Hospital criteria. **Methods:** Of the 956 patients with prostate cancer who met the Royal Marsden Hospital criteria for AS underwent radical prostatectomy between January 2006 and June 2014, we enrolled the 830 patients whose pGS was $\leq$ 3+4 in analysis. We stratified the patients into 3 groups according to the disparity between the bGS and pGS, as follows: group A (n = 211): bGS 3+3 to pGS 3+3; group B (n = 430): bGS 3+3 to pGS 3+4; group C (n = 189): bGS 3+4 to pGS 3+4. **Results:** The patients in group C had a higher preoperative prostate-specific antigen level, a higher percentage of positive cores, maximum core involvement ($P < .001$), and higher postoperative levels of extracapsular extension, seminal vesicle invasion, and positive surgical margins compared with the patients in groups A and B ($P < .001$, $P = .002$, and $P < .001$, for patients in groups C, B, and A, respectively). Group C had a significantly lower BCR-free survival rate compared with groups A and B via Kaplan-Meier, and no difference was observed in the BCR between groups A and B (log rank, $P = .475$). **Conclusion:** Although the patients with the same pGS 3+4 after RP, different adverse outcomes were observed. Because of the significantly different prognosis based on the presence of Gleason pattern 4, patients with this pattern are not suitable for AS.

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Introduction

The detection of insignificant prostate cancer (PCa) has increased over the past 2 decades because of the screening for prostate-specific antigen (PSA).[1] Although PSA screening can reduce the spread and mortality of PCa, it can also lead to an increase in the over-diagnosis of low-risk PCa. Due to the potential side effects of the treatment, it is critical that not all patients with PCa receive aggressive treatment.[2] In some cases, active surveillance (AS) has emerged as a treatment option for patients with low-risk PCa. AS can lead to a reduction in the potential side effects from the treatment with the opportunity for a

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curative treatment if the PCa progresses.[3-5] AS has evolved as a treatment strategy to prevent overtreatment of low-risk PCa.

In previous studies, patients with low-risk PCa did not demonstrate a significantly worse survival when they were subjected to AS compared with surgical treatment or radiation therapy.[6,7] Dall'Era et al reviewed seven representative criteria for AS and showed that the inclusion criteria for surveillance vary among studies. In addition, they reported that PCa-specific mortality remains low (0%-1%) even with varied inclusion criteria; they found that the longest published median follow-up was 6.8 years.[8]

It is debatable whether some strict criteria for AS may exclude candidates for AS due to rigorous inclusion factors. Because spreading AS is a treatment option for patients with low-risk PCa, some reports have suggested an expansion of the criteria for AS.[9,10] Other reports have suggested that AS may also be possible for a select group of patients with intermediate-risk PCa.[11] Previous studies have also suggested that the eligibility for AS might be extended to selected patients with a biopsy Gleason score (bGS) 3+4 PCa. El Hajj et al reported that patients with a bGS 3+4 as candidates for AS were more likely to have unfavorable PCa that remained undetected, and thus, they suggested a restriction to older patients with comorbidities.[11] However, no consensus has been reached as to how to select candidates for AS among these patients.[12-15]

Moreover, younger patients who are candidates for AS can be treated with curative treatment if significant risk of upgrading is identified in patients with a bGS 3+3.

We hypothesized that biochemical outcomes can be affected according to their original Gleason pattern, especially pattern 4. The Royal Marsden Hospital (RMH) criteria for AS is the representative criteria that is included in pattern 4. Therefore, we selected the RMH criteria for AS in this study. We identified the features of patients who may be candidates for AS through the analysis of the biochemical outcomes after radical prostatectomy (RP) in Asian population.

Moreover, the prediction of upgrading from bGS 3+3 to pathologic Gleason score (pGS) 3+4 may help to select candidates for AS among patients with biopsy-proven GS 3+3 or 3+4 PCa.

Materials and Methods

Study Population

After receiving Institutional Review Board approval, we reviewed the records of 2042 patients who underwent an RP at Seoul National University Bundang Hospital from January 2006 to June 2014. We only included men who underwent RP from 2006 to eliminate the effect of the modifications of Gleason grading system by International Society of Urological Pathology (ISUP) in 2005.[16] From these, we identified 956 patients who met RMH criteria for AS: clinical stage $\leq$ T2a, PSA $\leq$ 15, GS $\leq$ 3+4, and total positive core number percentage $\leq$ 50%.[17] We excluded the patients whose pGS was $\geq$ 4+3 after RP and also excluded the patients whose files were missing clinical and pathologic information. Accordingly, we finally enrolled the 830 patients in this analysis.

For our study, patients who met the RMH criteria for clinically insignificant PCa and who had a bGS 6 (3+3) to pGS 6 (3+3) were designated as group A (n = 211), while those who met the RMH criteria for clinically insignificant PCa and had a bGS 6 (3+3) to pGS 7 (3+4) were designated as group B (n = 430); those who met the RMH criteria for clinically insignificant PCa and had a bGS 7 (3+4) to pGS 7 (3+4) were designated as group C (n = 189). Only 3 patients were observed as downgrading (from bGS 3+4 to pGS 3+3) with meeting RMH criteria for AS; we excluded this downgrading group.

Histopathological Analysis

A single experienced uro-pathologist (Prof. Gheeyoung Choe) examined prostate specimen obtained from transrectal ultrasonography (TRUS)-guided prostate biopsy and RP. Adverse pathologic features were defined as an extracapsular extension (ECE) of the tumor, seminal vesicle invasion (SVI), lymph node invasion (LNI), and positive surgical margins (PSM). PSM are affected by surgeon's experience. In our institution, we performed 400 robotic surgeries in last year, and the data on analysis included patients of high-volume surgeons. Adverse pathologic outcomes were also analyzed by the chi-square test. We performed lymph node (LN) dissection in 193 patients with bGS 6, and other patients with bGS did not have LN dissection. Karl et al analyzed the risk of biochemical recurrence (BCR) among pT3aNo/Nx PCa.[18] In that study, they found LN status was not an independent predictor of BCR. Therefore, we consider the non-LN dissection group as non-LNI.

Outcome Measurements and Statistical Analysis

For each patient, the following clinical features were considered: age, body mass index, diabetes mellitus, hypertension, Charlson comorbidity index (CCI), prostate-specific antigen (PSA), prostate volume (as measured by trans-rectal ultrasound), PSAD (ng/ml per gram), biopsy-positive core number percentage (PCNP), and maximum core involvement percentage (MCIP). Maurice et al assessed the impact of CCI in patients with eligibility for AS. They analyzed upgrading and upstaging according to binary CCI score ($\leq$ 1, $>$ 1).[19] The characteristics of the patients were analyzed by analysis of variance and chi-square tests. We conducted PSA, International Prostate Symptom Score (IPSS), International Index of Erectile Function (IIEF), uroflowmetry, and continence questionnaire (pad usage) at postoperative 3 months, 6 months, 12 months. We also conducted an annual PSA check if there was no BCR. If there was BCR, we conducted image work-up including computed tomography scan and magnetic resonance imaging (MRI). BCR was defined as a PSA value $\geq$ 0.2 ng/mL on 2 consecutive measurements.[20] BCR-free survival was analyzed with the Kaplan-Meier method. Cox univariate and multivariate regression models were used to identify the predictors of BCR in the RMH criteria for AS. SPSS v. 22.0 was used for all statistical analyses, and we defined a P value of $<$ .05 as statistically significant.

Results

Patient characteristics are given in Table 1. In our cohort of 830 men, 430 (51.8%) were upgraded at the time of surgery. Each group showed different characteristics with respect to age, PSA level, prostate volume, PSA density, PCNP, and MCIP. Group C showed a higher level of PSA and higher PCNP and MCIP ($P <$ .001) compared with the other 2 groups. In group C, the PSA level was higher (0.6-1.2 ng/mL) than in groups B and A, and the PCNP and