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ORIGINAL ARTICLE

Prostate Cancer

Analysis of expanded criteria to select candidates for active surveillance of low-risk prostate cancer

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We aimed to analyze the value of each criterion for clinically insignificant prostate cancer (PCa) in the selection of men for active surveillance (AS) of low-risk PCa. We identified 532 men who were treated with radical prostatectomy from 2006 to 2013 who met 4 or all 5 of the criteria for clinically insignificant PCa (clinical stage \leq T1, prostate specific antigen [PSA] density \leq 0.15, biopsy Gleason score \leq 6, number of positive biopsy cores \leq 2, and no core with $>$ 50% involvement) and analyzed their pathologic and biochemical outcomes. Patients who met all 5 criteria for clinically insignificant PCa were designated as group A ($n = 172$), and those who met 4 of 5 criteria were designated as group B ($n = 360$). The association of each criterion with adverse pathologic features was assessed via logistic regression analyses. Comparison of group A and B and also logistic regression analyses showed that PSA density $>$ 0.15 ng ml $^{-1}$ and high (≥ 7) biopsy Gleason score were associated with adverse pathologic features. Higher ($>$ T1c) clinical stage was not associated with any adverse pathologic features. Although ≤ 3 positive cores were not associated with any adverse pathology, ≥ 4 positive cores were associated with higher risk of extracapsular extension. Among potential candidates for AS, PSA density $>$ 0.15 ng ml $^{-1}$ and biopsy Gleason score $>$ 6 pose significantly higher risks of harboring more aggressive disease. The eligibility criteria for AS may be expanded to include men with clinical stage T2 tumor and 3 positive cores.

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INTRODUCTION

With the increasing concerns related to the overdiagnosis and overtreatment of prostate cancer (PCa), the interest in conservative management approaches of active surveillance (AS) has been increasing rapidly.^{1–3} Although questions still remain regarding its efficacy and safety, AS is currently included as a treatment option in the guidelines for the management of localized PCa published by the European Association of Urology, the American Urological Association, and the National Comprehensive Care Network.^{4–6}

Certainly, many of the published criteria used for the identification of men who are eligible for AS are based on Epstein criteria for clinically insignificant PCa (clinical stage \leq T1, prostate specific antigen [PSA] density \leq 0.15 ng ml $^{-1}$ cm $^{-3}$, biopsy Gleason score \leq 6, number of positive biopsy cores \leq 2, and no core with $>$ 50% involvement).⁷ Today, various institutions apply different eligibility criteria for AS.^{8–11} When these criteria are compared, there may well be a clear trade-off between sensitivity and specificity for predicting insignificant PCa. Meanwhile, it remains to be determined whether the application of most conservative criteria is optimal.¹² The accurate identification of men with insignificant disease still remains a challenging goal.

The increased use of the PSA test along with lowering of the PSA thresholds for biopsy may have contributed to a higher proportion of men diagnosed with disease that is amenable to AS. It has been suggested that stricter criteria for AS may unnecessarily exclude potential candidates for AS. Accordingly, efforts to expand the criteria for AS have been reported.^{13,14} Despite the fact that AS was

initially devised to provide conservative management of patients with very-low-risk or low-risk PCa, some have even reported that AS may be suitable for a select group of patients with intermediate-risk PCa.¹⁵ As most of the conservative inclusion criteria for AS limit the number of candidates for this approach, it would be important to search for criteria to safely expand the pool of candidates for AS. It would be only appropriate that such effort should start by evaluating each widely used criterion for identifying men who are candidates for AS. Thus, we performed a comparative analysis of the outcomes of patients who met all 5 criteria for clinically insignificant PCa, which is considered the backbone of many AS eligibility criteria used today, and those who met all but one criterion with the aim of assessing the value of each eligibility criterion in the prediction of outcomes among the men with low-risk PCa.

MATERIALS AND METHODS

With approval from our Institutional Review Board, we reviewed the records from our radical prostatectomy (RP) database of 1908 patients who underwent RP from 2006 to 2013 at our institution. Among these men, we identified those who met all of the following 5 criteria for clinically insignificant PCa and also those who met 4 of the 5 criteria: PSA density less than 0.15 ng/mL/cm 3 , clinical stage \leq T1c, Gleason sum 6 or less, and 2 or fewer cores positive with no more than 50% of a core involved. After excluding patients who did not meet 2 or more criteria ($n = 1369$) and those with missing data relevant to any of the five criteria ($n = 7$), a total of 532 patients were included in our

study. To analyze the clinical significance of each criterion, subgroup analyses were performed according to the criterion that was not met, if any, by each patient.

For our study, patients who met all 5 criteria for clinically insignificant PCa were designated as group A, and those who met 4 of 5 the criteria were designated as group B. We evaluated various clinicopathologic variables in all subjects. PSA density was calculated via prostate volume assessed using transrectal ultrasound (TRUS). Adverse pathologic features analyzed from RP specimens include extracapsular tumor extension (ECE), seminal vesicle invasion, and high pathological Gleason score ($\geq 4 + 3$). For our study, we defined significant tumor as nonorgan confined disease or a pathological Gleason score $\geq 4 + 3$. The analysis of postoperative biochemical outcome following RP was limited to patients who underwent RP from 2006 to 2011. Biochemical recurrence (BCR) was defined as a PSA value ≥ 0.2 ng ml⁻¹ on two consecutive measurements.

The characteristics of patients were analyzed by using Student's *t*-test and chi-square test. Chi-square analysis was used to compare the rates of adverse pathologic outcomes between patient groups. Logistic regression analyses were performed to analyze the association of each clinical variable with adverse pathologic features. Postoperative BCR-free survivals of the patient groups were calculated and compared using the Kaplan–Meier method. SPSS version 20.0 (IBM, New York, USA) was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of our subjects are listed in **Table 1**. Of 532 total patients included in our study, 172 (32.33%) men fulfilled the Epstein criteria for clinically insignificant PCa (group A) while 360 (67.67%) met 4 of the 5 criteria (group B). In group A and B, biopsy with 12 or more cores was performed in 91.3% and 89.5% of the patients, respectively. In group B, 50 (13.89%) patients met 4 criteria but had clinical stage \geq T2a. Additionally, 210 (58.33%) patients in group B had PSA density > 0.15 ng ml⁻¹ cm⁻³. A total of 36 (10.00%), 57 (15.83%), 7 (1.94%) patients in group B had a biopsy Gleason score > 6 , number of positive cores > 2 , and cancer involving $> 50\%$ of a biopsy core, respectively. Comparing group A and B, there were significant differences in PSA, PSA density, biopsy Gleason score, number of positive cores, and percentage core involvement (all $P < 0.001$) (**Table 1**). When comparing pathologic outcomes, the two groups showed significant differences in the rates of ECE ($P = 0.001$), high pathologic Gleason score ($P = 0.037$), and significant tumor ($P < 0.001$).

Regarding the adverse pathologic features in group A and B, no significant difference in any adverse pathologic outcome was observed between groups A and patients of group B who had clinical stage $> T1c$ (all $P > 0.05$) (**Table 2**). Compared with group A, group B patients with PSA density > 0.15 ng ml⁻¹ cm⁻³ or biopsy Gleason score > 6 had significantly higher rates of 2 or more adverse pathologic features, including significant tumor (both $P < 0.001$). Comparing patients in group A with group B patients with PSA density of 0.15 ng ml⁻¹ cm⁻³ to 0.20 ng ml⁻¹ cm⁻³, a significant difference in the rate of ECE was observed (4.6% vs 13.8%, $P = 0.003$). Group B patients who had 3 or more positive biopsy cores did not show significantly higher risk of any adverse pathology compared with group A (all $P > 0.05$). Because the number of group B patients with $> 50\%$ core involvement was only 7, comparing adverse pathologic outcomes of these men and those of the group A was not deemed appropriate.

The results of multivariable logistic regression analysis of the associations between each of the 5 criteria for clinically insignificant

PCa and adverse pathological features are shown in **Table 3**. High PSA density was associated with ECE and significant tumor. In addition, high biopsy Gleason score was associated with high pathological Gleason score and significant tumor. In contrast, advanced clinical stage was not associated with any adverse pathologic features. Meanwhile, although men with 3 positive cores were not associated with any adverse pathology, those with 4 or more positive cores were shown to be associated with higher risk of ECE. Although higher percent core positivity was associated with higher risk of ECE, the number of patients with $> 50\%$ core positivity was too small as mentioned above.

Regarding postoperative BCR-free survival, group A and B demonstrated no significant difference during a mean follow-up period of 49.62 months (median 49) (log rank $P = 0.418$). When group B was sub-stratified according to the criterion for clinically insignificant PCa not met by each patient, 5 subgroups showed no significant differences in biochemical outcomes compared with a group A (log rank $P = 0.080$). Because the two variables of PSA density and biopsy Gleason score were the criteria that were most strongly associated with adverse pathologic features compared with the other 3 criteria for clinically insignificant PCa, we re-analyzed BCR-free survivals after stratifying patients by PSA density (< 0.15 , 0.15–0.18, 0.19–0.23,

Table 1: Characteristics of patients by group

Variables	Group A (n=172)	Group B (n=360)	P
Age, year	65.77±6.52	65.33±6.64	0.467
BMI, kg m ⁻²	24.49±2.42	24.31±2.66	0.447
PSA	4.76±1.75	7.76±6.2	<0.001
Prostatic volume	47.13±17	39.6±15.39	<0.001
PSAD, ng ml ⁻¹ cm ⁻³	0.104±0.29	0.210±0.17	<0.001
Biopsy Gleason score, n (%)			
≤6	172 (100)	324 (90.0)	<0.001*
7 (3+4)	0	25 (6.9)	
7 (4+3)	0	9 (2.5)	
≥8	0	2 (0.6)	
Biopsy positive core number	1.33±0.47	1.78±1.24	<0.001

[†] χ^2 -test; Group A: active surveillance; Group B: active surveillance except one factor; BMI: body mass index; PSA: prostate specific antigen; PSAD: prostate specific antigen density

Table 2: Correlation between each group and adverse pathologic outcomes

Variables	Extracapsular tumor extension	Seminal vesicle invasion	Pathological Gleason score ≥ 7 (4+3)	Significant tumor [†]
Group A (n=178)	4 (2.3)	0	7 (4.1)	10 (5.8)
Stage greater than cT1 (n=50)	2 (4.0)	0	2 (4.0)	4 (8.0)
P	0.52		0.982	0.576
PSAD > 0.15 ng ml ⁻¹ cm ⁻³ (n=210)	26 (12.4)	1 (0.5)	12 (5.7)	37 (17.6)
P	<0.001	0.365	0.462	<0.001
Biopsy Gleason score > 6 (n=36)	2 (5.6)	1 (2.8)	14 (38.9)	14 (38.9)
P	0.292	0.028	<0.001	<0.001
3 or more positive cores (n=57)	5 (8.8)	0	3 (5.3)	7 (12.3)
P	0.03		0.702	0.107
$> 50\%$ core positive (n=7)	2 (28.6)	0	2 (28.6)	2 (28.6)
P	<0.001		0.004	0.018

χ^2 -test; Group A: active surveillance. [†]Nonorgan confined or pathological Gleason score 7 (4+3) or greater. PSA: prostate specific antigen; PSAD: prostate specific antigen density



Table 3: Logistic regression analysis of Epstein criteria for clinically insignificant cancer and adverse pathologic outcome in patient who met 4 of the 5 criteria

	Extracapsular tumor extension		Seminal vesicle invasion		Pathological Gleason score ≥ 7 (4+3)		Significant tumor ^a	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Clinical stage								
T1	Reference		Reference		Reference		Reference	
T2a	1.998	0.435	0.874	1	1.11	0.898	1.604	0.444
T2b or greater	0		1.828	1	0	0.999	0	0.999
PSAD (ng ml ⁻¹ cm ⁻³)								
<0.15	Reference		Reference		Reference		Reference	
0.15-0.18	5.664	0.01	1.215	1	0.475	0.492	2.619	0.067
0.19-0.23	6.4	0.003	1.132	1	2.124	0.215	4.466	0.001
>0.23	5.439	0.005	Inf.	0.995	1.44	0.531	3.19	0.007
Biopsy place								
SNUBH	Reference		Reference		Reference		Reference	
Other clinic	1.74	0.124	0	0.996	1.634	0.22	1.691	0.07
Biopsy Gleason score								
<6	Reference		Reference		Reference		Reference	
7 (3+4)	1.488	0.729	1.111*	0.995	6.549	0.002	4.451	0.01
7 (4+3)	5.335	0.155	1.05	1	49.126	<0.001	33.847	<0.001
8 or greater	0		0.757	1	4.392*	0.999	3.046*	0.999
Positive core number								
1-2	Reference		Reference		Reference		Reference	
3	1.601	0.679	0.919	1	2.897	0.141	1.996	0.319
4	7.26	0.031	0.829	1	0	0.999	2.782	0.217
5 or greater	7.741	0.027	1.065	1	0	0.999	2.985	0.192
Maximum core positive %								
<50	Reference		Reference		Reference		Reference	
51-60	12.227	0.049	1.828	1	6.985	0.114	4.751	0.198
61-75	0		0.757	1	0	1	0	1
>75	28.348	0.028	Inf.	1	16.644	0.06	11.153	0.1

^aNonorgan confined or pathologic Gleason score 7 (4+3) or greater; *Insufficient outcomes. OR: odds ratio; CI: confidence interval; PSA: prostate specific antigen; SNUBH: Seoul National University Bundang Hospital; PSAD: prostate specific antigen density

and > 0.23) and biopsy Gleason score (3 + 3, 3 + 4, 4 + 3, and ≥ 8). No significant differences in biochemical outcome were observed when patients were stratified according to PSA density (log rank, $P = 0.578$). Comparison of the men with PSA density < 0.15 ng ml⁻¹ cm⁻³ and those with PSA density of 0.15 ng ml⁻¹ cm⁻³ to 0.20 ng ml⁻¹ cm⁻³ revealed, no significant differences regarding biochemical outcome (log rank, $P = 0.973$). However, BCR-free survivals were significantly shorter for men with biopsy Gleason score 4 + 3 compared with those with 3 + 3 (log rank, $P < 0.001$). Meanwhile, no significant differences in biochemical outcome were observed between men with Gleason 3 + 4 and 3 + 3 tumors (log rank $P = 0.603$). Additionally, no significant differences in biochemical outcome were noted between group A and the men in group B stratified according to the number of positive cores (log rank $P = 0.568$).

DISCUSSION

By analyzing each criterion for predicting insignificant PCa, which also make up many different eligibility criteria for AS, we observed that biopsy Gleason score > 6 and PSA density > 0.15 ng ml⁻¹ cm⁻³ were the most strongly associated with adverse pathologic features amongst potential candidates for AS. In contrast, higher (> T1c) clinical stage was not associated with adverse pathology in the potential candidates for AS. Meanwhile, the number of positive cores was shown to be less associated with adverse pathology than biopsy Gleason score and PSA density. Our results suggested that men with up to 3 positive cores

who met all other criteria for clinically insignificant PCa could safely be enrolled onto an AS program. Due to the relatively smaller number of patients with higher percent core involvement, an appropriate evaluation of this criterion was not feasible in this study.

Previously Reese *et al.*¹⁶ performed a study to determine the relative importance of the same AS eligibility criteria evaluated in our study. Analyzing men treated with RP between 1995 and 2012 who met 4 or more of the 5 criteria, they found that PSA density > 0.15 ng ml⁻¹ cm⁻³ and biopsy Gleason score ≥ 7 were strongly associated with adverse pathological findings at RP. Based on their findings, they suggested that AS criteria should be expanded to include men with clinical stage T2 lesions and a greater number of positive biopsy cores of low grade. Overall, their findings correspond highly with our findings. Other published series have shown similar findings on the criteria of clinical stage for AS eligibility.^{16,17} Accordingly, several western institutions enroll men with clinical stage T2 tumors on AS.¹² In their series, Reese *et al.*¹⁴ found that men with 3 positive biopsy cores and 50%–60% core involvement who met all other criteria are suitable candidates for AS. Although we could not perform adequate analysis on the criterion of percentage core involvement, men with 3 positive cores were also not associated with significantly higher risk of adverse pathology at RP or worse biochemical outcome compared with those with 1 or 2 positive cores in our study. The results of our study confirmed several findings from the study by Reese *et al.* On the other hand, there were notable differences in study design between the two studies. First, Reese *et al.*

had to exclude more than half of the men included in their RP series upfront due to missing clinical data. Second, 12 or more biopsy cores were obtained in more than 85% of the patients in our study whereas only approximately 20% had biopsy with 12 or more cores in the Reese *et al.*'s study. Third, we used prostate volume measured via preoperative TRUS or magnetic resonance imaging to calculate the PSA density as is typically performed in actual clinical settings whereas prostate volume estimated from RP specimen weight was used to calculate the PSA density in the Reese *et al.*'s study. Despite the difference in the size of the patient cohort, we believe that our cohort, which is more contemporary, may be more appropriate for the proper evaluation of AS eligibility criteria, which are preoperative clinical variables that mostly biopsy-related.

Currently, AS is still considered to be underused in western countries. Meanwhile, it is even less frequently employed in Asia. Except for only a few anecdotal cases, the number of patients formally enrolled in an AS program at our institution was low during the study period. In addition, radiotherapy was seldom recommended for low-risk PCa at our institution. Due to such circumstances, our subjects may be considered representative of almost all of the potential candidates for AS managed at our institution during the study period. As the number of men undergoing AS is increasing in western institutions,¹⁸ the possibility of selection bias should be considered in the interpretation of contemporary RP series on potential candidates for AS reported from large, western institutions.

Among our subjects, only 172 of 1908 (approximately 9%) from total RP series would have been deemed suitable for AS if original Epstein criteria were used as the AS eligibility criteria at our institution during the study period. The fact that PSA testing is relatively less prevalent in Asia than in western countries may have, at least partly, contributed to such a low rate of favorable disease among our RP cohort. Meanwhile, if the criteria were expanded according to our findings, 50 men with clinical stage \geq T2 and 29 men with 3 positive cores would have been additionally considered appropriate for AS (45.93% increase). Such a finding would certainly be clinically significant considering that these additional men would be spared of the morbidities from unnecessary radical treatments with the expansion of criteria.

Regarding the discrimination between biopsy Gleason score of 3 + 3 and 3 + 4, a significantly higher rate of adverse pathologic features at RP among our subjects with biopsy Gleason 3 + 4 tumor would support the exclusion of these men from AS programs. Meanwhile, others mentioned that select patients with Gleason 3 + 4 tumor can be considered for AS. Moreover, we observed no significant difference in BCR-free survivals between group A and those in group B with Gleason 3 + 4 tumor during a mean follow-up duration of approximately 50 months. Nevertheless, biochemical outcome may have been different with longer follow-ups. Because pathologic and biochemical outcomes can only be considered as surrogates for long-term outcomes (metastasis-free or disease-specific survival), we admit that inherent limitations would exist regarding the interpretations of our findings.

Recently, efforts have been made to integrate the state-of-the-art methods of genetic assays to identify appropriate candidates for AS. The cell cycle progression signature test (Prolaris) is a gene expression based assay that directly measures tumor growth capacity allowing the stratification of patients with localized PCa according to cancer aggressiveness.¹⁹⁻²¹ This test combines the gene expression levels of 31 genes associated with cell cycle progression and 15 housekeeping genes into a cell cycle progression score that can be used to predict the risk of BCR, metastasis, and cancer-specific mortality. Similarly, a multi-gene,

real-time polymerase chain reaction (RT-PCR) assay (Oncotype DX Assay) has been developed.²² This assay includes 5 reference genes and 12 cancer genes representing distinct biological pathways with a known role in prostate tumorigenesis. Reference normalized expression of 12 cancer-related genes is used to calculate the so called Genomic Prostate Score which can be used to predict adverse pathologic features beyond conventional variables. Although still not widely adopted, it is hoped that new assays that utilizing molecular biomarkers would complement conventional clinical and pathological parameters to personalize the care of cancer patients. Meanwhile, regardless of the advancement in diagnostic tools, studies on the prediction of outcomes or the selection of candidates for AS can only be problematic until long-term follow-up data on AS become available.

Our study may be limited by its retrospective nature. Though many different versions of AS eligibility criteria are currently used, only items included in the Epstein criteria were evaluated in this study. Although the number of our subjects is relatively small compared with other similar series, it should be noted that we excluded men who underwent RP before 2006 to minimize the effect from the modifications of Gleason grading system introduced by the International Society of Urological Pathology in 2005.²³ Because our series is only based on men who underwent RP, our findings may not be representative of men who underwent other forms of treatment, such as radiotherapy. In addition, data on tumor volume from RP specimens were not available in our subjects.

AUTHOR CONTRIBUTIONS

JKJ and SKH participated in the design of the study, conducted the data acquisition, interpreted and statistically analyzed the data and drafted the manuscript. SKH revised the manuscript critically for important intellectual content. HSL and YIL performed the data acquisition. SEL designed the study and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

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