



Predicting Insignificant Prostate Cancer: Analysis of the Pathological Outcomes of Candidates for Active Surveillance according to the Pre-International Society of Urological Pathology (Pre-ISUP) 2014 Era Versus the Post-ISUP2014 Era

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Purpose: To analyze the difference in the prediction accuracy with an active surveillance (AS) protocol between two eras (pre-International Society of Urological Pathology [pre-ISUP]-2014 vs. post-ISUP2014).

Materials and Methods: We retrospectively analyzed 118 candidates for AS who underwent radical prostatectomy between 2009 and 2017. We divided our patients into two groups (group 1 [n=57], operation date 2009–2015; group 2 [n=61], operation date 2016–2017). Pathologic slides in group 1 were reviewed to distinguish men with cribriform pattern (CP) because the determination of Gleason scores in old era had been based on pre-ISUP2014 classification. Postoperative outcomes in the two eras were analyzed twice: first, all men in group 1 vs. group 2; second, the remaining men after excluding those with CPs in group 1 vs. group 2.

Results: The proportion of men with insignificant prostate cancer (iPCa) was significantly lower in group 1 than in group 2 (36.8% vs. 57.4%, p=0.040). After excluding 11 men with CPs from group 1, those remaining (46 men) were compared again with group 2. In this analysis, the proportion of men with iPCa was similar between the two groups (old vs. contemporary era: 41.3% vs. 57.4%, p=0.146). Nine of 11 men with CP had violated the criteria for iPCa in the earlier comparison.

Conclusions: The accuracy of the AS protocol has been affected by the coexistence of CPs and pure Gleason 6 tumors in the pre-ISUP2014 era. We suggest to use only contemporary (post-ISUP2014) data to analyze the accuracy with AS protocols in future studies.

Keywords: Neoplasm grading; Prostatectomy; Prostatic neoplasms; Watchful waiting

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INTRODUCTION

Active surveillance (AS) is a management strategy in a superselect group of low-risk prostate cancer patients, involving close monitoring of the course of disease with the expectation to intervene if the cancer progresses. The goal of AS is to minimize overtreatment for indolent disease, and to defer treatment and its potential adverse effects. Currently, several AS criteria have been proposed [1-5].

However, the risk of AS has also been highlighted because there have been reports on adverse features in radical prostatectomy (RP) specimens from men who initially fulfilled the preoperative AS criteria. Such misclassification results in the possibility of missing an opportunity for cure, or the progression or metastasis of the cancer before treatment. Ploussard et al [6] reported that the rate of upgrading of Gleason score (GS) and pathological upstaging was up to 42% in patients who were initially considered to have insignificant prostate cancer according to Epstein criteria. Lee et al [7] reported that even the most stringent AS criteria were not able to fully discriminate low-risk patients from those affected by clinically significant prostate cancer. In an effort to reduce such misclassification, the use of other modalities such as multiparametric magnetic resonance imaging (mpMRI) in combination with the AS protocol is currently being investigated. Although mpMRI might be a promising tool for selecting AS candidates, some limitations remain with regard to its sensitivity and specificity [8-16].

In the 2014 consensus meeting, the International Society of Urological Pathology (ISUP) assigned Gleason pattern 4 to all cribriform patterns (CPs), based on the findings that any CP in prostate cancer is associated with a less favorable outcome, such as extraprostatic extension (EPE) and positive surgical margin (PSM) [17-19]. These changes resulted in a grade shift, in that many cases that used to be graded GS 6 are now graded GS 7. Consequently, the current GS 6 cases (so-called 'pure' GS 6 in the post-2014 ISUP era) are a homogeneous group of tumors lacking CPs and have a less aggressive nature, in contrast to GS 6 tumors of the original GS system era (pre-2014 ISUP era).

Accordingly, we hypothesized that the accuracy for predicting insignificant prostate cancer with the AS protocol can be different according to the study era. As there is a paucity of studies on this issue at present,

we aimed to analyze the difference in the prediction accuracy between the two eras (pre-ISUP2014 vs. post-ISUP2014).

MATERIALS AND METHODS

1. Ethics statement

This study was approved by the Institutional Ethics Committee of Yonsei University College of Medicine after reviewing the study protocol and procedures (Reg. No. 4-2018-1111). The requirement for written consent was waived because of the retrospective nature of the study. The data were anonymized before the analysis.

2. Demographics and clinicopathological data

A total of 675 consecutive patients with localized or locally advanced prostate cancer treated with RP at Yonsei Severance Hospital between 2009 and 2017 were selected. Of these individuals, patients with incomplete medical records were excluded. Patients who had pre-operative androgen deprivation or radiation therapy were also excluded. With respect to the number of total biopsy cores, we excluded men who did not undergo a 12-core biopsy. This resulted in a study population of 637 men.

We used the Prostate Cancer Research International: Active Surveillance (PRIAS) protocol to select candidates for AS, because this protocol is the most appropriate for Asian patients with prostate cancer among five Western protocols (Johns Hopkins Medical Institutions [1], Memorial Sloan-Kettering Cancer Center [2], University of California at San Francisco [3], PRIAS [4], and University of Miami [5]), according to several authors [20,21]. The PRIAS protocol consists of GS 6 or less on biopsy, clinical stage T2 or less, prostate specific antigen (PSA) 10 ng/mL or less, PSA density (PSAD) 0.2 ng/mL/cm³ or less and no more than 2 positive cores. On the basis of these criteria, we identified a total of 118 candidates for AS. We divided these patients into two groups according to the date of operation: group 1 (n=57, operation date 2009–2015, old era) and group 2 (n=61, operation date 2016–2017, contemporary era), because the modified GS system (released in the 2014 ISUP consensus meeting) has been applied at Yonsei Severance Hospital since 2016.

We obtained data on patient demographics and clinical characteristics, including age, prostate volume

on transrectal ultrasound, preoperative PSA values, PSAD, number of positive biopsy cores, clinical/pathological T stage, biopsy/pathological GS, and pathological tumor volume.

For clinical staging, all patients underwent prostate MRI using a 3.0-T MRI system (Intera Achieva 3.0 T; Phillips Medical System, Latham, NY, USA) at 3–4 weeks after prostate biopsy and before surgery. MRI included T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging. T2-weighted images were acquired in three orthogonal planes (axial, sagittal, and coronal). From the diffusion-weighted imaging data, the apparent diffusion coefficient map was generated, with b values of 0 and 1,000 s/mm², by using the mono-exponential model. All mpMRIs were reviewed using the Prostate Imaging Reporting and Data System (PI-RADS) ver. 2.

All RP specimens were weighed, inked, fixed overnight in ambient formalin, cut at 3 mm intervals, and submitted as quadrants. To determine tumor volume in each nodule, slides were photocopied in a background of 1 mm² grid, and the amount of mm² in each tumor nodule was manually counted. To convert square into cubic millimeters, the total number of mm² was multiplied by 3 (thickness of prostate tissue sections) and 1.12 (fixation shrinkage factor). The nodule with the highest GS or the largest nodule (if nodules were the same grade) was considered dominant. All the processing was performed by an experienced genitourinary patholo-

gist (NHC). Insignificant prostate cancer was defined as organ-confined, GS 6 disease with a dominant tumor nodule volume of <0.5 cm³ [22].

3. Study endpoint

The main objective of this study was to compare the accuracy of the AS protocol for predicting insignificant prostate cancer, when data from the old era *vs.* the contemporary era were applied. A flow diagram illustrating our study design is shown in Fig. 1.

4. Reviewing the Gleason scores of patients in the old (pre-International Society of Urological Pathology-2014) era

Because the determination of GSs in group 1 had been based on the pre-ISUP2014 classification system, we needed to recheck all pathological slides in group 1 to determine which patient had or did not have any CPs in their biopsy pathologies (G 3+3=6 tumors that were determined in the pre-ISUP2014 era). This evaluation was also performed by NHC. The diagnostic accuracy (sensitivity and specificity) of identifying CPs was identical between the two study eras by the same pathologist (NHC).

5. Statistical analyses

The patients' preoperative and pathological characteristics were calculated using means for continuous variables and proportions for categorical variables.

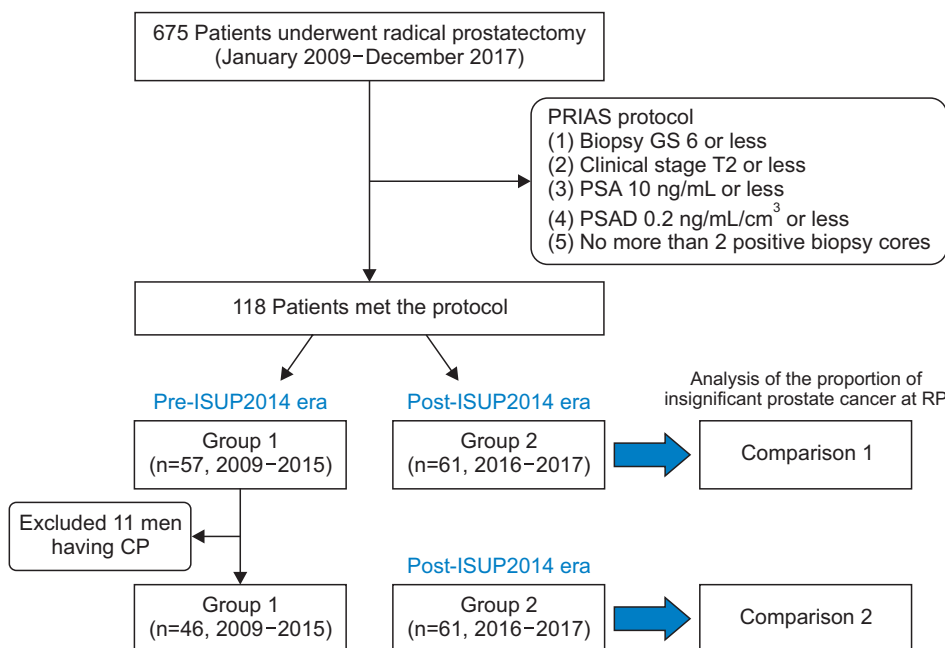


Fig. 1. Flow diagram illustrating study design. PRIAS: Prostate Cancer Research International: Active Surveillance, GS: Gleason score, PSA: prostate specific antigen, PSAD: prostate specific antigen density, ISUP: International Society of Urological Pathology, RP: radical prostatectomy, CP: cribriform pattern.

Student's t-test and Mann–Whitney–Wilcoxon test were used for continuous variables, and the chi-square test and Fisher's exact test were used to compare categorical variables between groups. Multivariate logistic regression models that included all collected variables were constructed to identify the predictors of insignificant prostate cancer. Statistical analyses were performed with R statistics ver. 3.5.1. Values of $p < 0.05$ were considered to indicate statistical significance.

RESULTS

Table 1 summarizes the baseline patient characteristics. There were no significant differences in preoperative PSA value, prostate volume, PSAD, number of positive biopsy cores, and distribution of clinical T stages between the two groups. Age was higher in group 2 (61.9 ± 14.8 years vs. 66.7 ± 11.3 years, $p = 0.001$).

Postoperatively, the proportion of insignificant pros-

Table 1. Preoperative patient characteristics

Characteristic	Group 1 (pre-ISUP2014 era; n=57)	Group 2 (post-ISUP2014 era; n=61)	p-value
Age (y)	61.9±14.8	66.7±11.3	0.001 ^a
PSA (ng/mL)	5.20±0.28	4.98±0.07	0.486 ^a
Prostate volume (cm ³)	39.9±10.5	40.5±2.6	0.830 ^a
PSAD (ng/mL/cm ³)	0.14±0.03	0.13±0.02	0.227 ^a
Positive biopsy cores (n)	1.24±0.0	1.40±0.0	0.068 ^a
Clinical T stage			0.681 ^b
cT1c	21 (36.9)	18 (29.5)	
cT2a/b	30 (52.6)	35 (57.4)	
cT2c	6 (10.5)	8 (13.1)	
PI-RADS v2			0.586 ^c
1–2	12 (21.0)	19 (31.1)	
3	16 (28.1)	17 (27.9)	
4	23 (40.4)	21 (34.4)	
5	6 (10.5)	4 (6.6)	

Values are presented as mean±standard deviation or number (%).

ISUP: International Society of Urological Pathology, PSA: prostate specific antigen, PSAD: prostate specific antigen density, PI-RADS: prostate imaging reporting and data system.

^aCalculated using Student's t-test or Mann–Whitney–Wilcoxon test.

^bCalculated using chi-square test.

^cCalculated using Fisher's exact test.

Table 2. Postoperative histopathological outcomes in the 2 groups

Variable	Group 1 (pre-ISUP2014 era; n=57)	Group 2 (post-ISUP2014 era; n=61)	p-value
Pathologic stage			0.114 ^a
pT2	42 (73.7)	53 (86.9)	
pT3	15 (26.3)	8 (13.1)	
Postoperative Gleason score			0.459 ^b
6	37 (64.9)	42 (68.9)	
7	18 (31.6)	19 (31.2)	
8–10	2 (3.5)	0 (0)	
Tumor volume (cm ³)	1.16±0.11	0.73±0.11	0.003 ^c
Organ confined Gleason score 6 disease	30 (52.6)	38 (62.3)	0.381 ^a
Insignificant prostate cancer	21 (36.8)	35 (57.4)	0.040 ^a

Values are presented as number (%) or mean±standard deviation.

ISUP: International Society of Urological Pathology.

^aCalculated using chi-square test.

^bCalculated using Fisher's exact test.

^cCalculated using Student's t-test.

tate cancer was 47.4% (56/118) in the overall cohort. Table 2 shows the postoperative histopathological outcomes for each group. The proportion of pT3 was 26.3% and 13.1% in group 1 and group 2, respectively (p=0.114). The distribution of postoperative GSs was similar between the two groups. The pathological tumor volume was higher in group 1 (1.16±0.11 cm³ vs. 0.73±0.11 cm³, p=0.003). The proportion of insignificant prostate cancer was significantly lower in group 1 than in group 2 (36.8% vs. 57.4%, p=0.040). Multivariate logistic regression analysis revealed the predictors of insignificant prostate cancer (Table 3). The study era was found to be an independent predictor of meeting the criteria for insignificant prostate cancer (odds ratio 3.01, 95% confidence interval 1.30–6.97, p=0.010).

We then rechecked all pathological slides in group 1 to distinguish patients harbouring CPs in their biopsy

Table 3. Multivariate logistic regression analysis of the prediction of insignificant prostate cancer

Variable	Odds ratio	95% CI	p-value
Age	0.95	0.89–1.01	0.076
Prostate volume	1.03	1.00–1.06	0.079
PSA	0.84	0.63–1.12	0.239
Clinical T stage			
cT1c	–	–	0.558
cT2a/b	0.91	0.39–2.11	
cT2c	1.00	0.27–3.79	
Study era			
Pre-ISUP2014	–	–	0.010
Post-ISUP2014	3.01	1.30–6.97	

CI: confidence interval, PSA: prostate specific antigen, ISUP: International Society of Urological Pathology.

specimen. When we reviewed a total of 57 pathologies in group 1, 11 patients (19.3%) had CP in their preoperative biopsy specimens. After we excluded these 11 men from group 1, the remaining men (46 patients) were compared again with group 2 for their histopathological outcomes (Table 4). In this analysis, there was no statistically significant difference in the proportion of insignificant prostate cancer between the two groups (old vs. contemporary era: 41.3% vs. 57.4%, p=0.146).

The analysis of men having CPs showed that 9 of the 11 patients had violated the criteria for insignificant prostate cancer in our earlier comparison (57 vs. 61 men). Table 5 shows the reasons for incorrect assignment to AS in the 11 patients.

Table 5. Reasons for incorrect assignment to active surveillance in 11 patients with cribriform pattern

Patients with cribriform pattern	Reasons for violation		
	Gleason score upgrading	T upstaging	Tumor volume >0.5 cm ³
Patient 1	+	+	+
Patient 2	+	-	+
Patient 3	-	+	+
Patient 4	+	-	+
Patient 5	-	-	+
Patient 6	-	+	+
Patient 7	+	+	+
Patient 8	-	-	+
Patient 9	+	-	+
Patient 10 (no violation)	-	-	-
Patient 11 (no violation)	-	-	-

Table 4. Postoperative histopathological outcomes in the 2 groups (after excluding 11 patients with cribriform pattern in group 1)

Variable	Group 1 (pre-ISUP2014 era; n=46)	Group 2 (post-ISUP2014 era; n=61)	p-value
Pathologic stage			0.233 ^a
pT2	35 (76.1)	53 (86.9)	
pT3	11 (23.9)	8 (13.1)	
Postoperative Gleason score			0.341 ^b
6	31 (67.4)	42 (68.9)	
7	13 (28.3)	19 (31.2)	
8–10	2 (4.3)	0 (0)	
Insignificant prostate cancer	19 (41.3)	35 (57.4)	0.146 ^a

Values are presented as number (%).

ISUP: International Society of Urological Pathology.

^aCalculated using chi-square test.

^bCalculated using Fisher's exact test.

DISCUSSION

The risk of AS has been highlighted because adverse features have been reported in RP specimens from men who were initially considered as having insignificant prostate cancer. Because of such misclassification, AS involves the possibility of missing an opportunity for cure, the possibility of progression or metastasis of the cancer before treatment, increased anxiety of living with untreated cancer, the need to undergo frequent examinations and prostate biopsies, and other disadvantages.

Despite recent efforts to improve the predicting power of AS (*e.g.*, by using a combination of mpMRI and the AS protocol), there are still limitations with respect to the accuracy. The UK National Institute for Health and Care Excellence is the first national body to recommend the use of MRI in men considering AS [8]. Tay et al [9] reported that combining mpMRI with the National Comprehensive Cancer Network low-risk clinical criteria resulted in a statistically significant improvement in specificity. Similarly, Schoots et al [10] reported that mpMRI at the beginning of AS can detect significant prostate cancer in 30% to 50% of men. However, although mpMRI is a promising tool, there are limitations that should be considered and not all studies have demonstrated a clear diagnostic benefit with mpMRI. For example, Mertan et al [12] reported that mpMRI during AS candidate selection has a relatively low specificity, especially in association with PI-RADS scores of 3 and 4. Concerning the false-negative results, Borofsky et al [13] reported that a small proportion of clinically important cancers can be missed or their size can be underestimated, depending on the quality of the scan and its interpretation. In one study, it was estimated that the negative predictive value of mpMRI considerably varies from 0.65 to 0.94 [14]. Similarly, as described in the 2018 European Association of Urology guidelines, the prostate cancer detection rate with mpMRI was reported to be rather low in GS 6 cancers and small lesions ($<0.5 \text{ cm}^3$) [15] in contrast to GS ≥ 7 cancers [16].

Accordingly, a limitation still exists concerning the accuracy for selecting the proper AS candidates despite recent attempts with the use of mpMRI. Under these circumstances, we paid attention to the modified 2014 ISUP grading system. A major point of divergence from the original GS system is with the assignment

of grade 4 to all CPs. Such modification was based on the recent findings that any cribriform morphology in prostate cancer is associated with a less favorable outcome. In 2011, it was reported that both large and small cribriform glands in RP specimens were associated with biochemical failure (BCF) [23]. In 2013, Dong et al [24] also demonstrated that the presence of a CP was an independent predictor for both BCF and metastasis after RP. In 2014, a series of articles showed CP to be associated with EPE, PSM, BCF, distant metastases, and disease-specific death [25,26]. In the 2014 ISUP consensus meeting in Chicago, 100% of the participants agreed that CPs should be assigned to Gleason pattern 4, regardless of morphology.

Therefore, a possible explanation may be that a certain proportion of men who were found to have GS 3+3=6 cancer in the pre-ISUP2014 era had harboured unfavorable features such as CPs, and this could be an important factor in the incorrect assignment to AS. That is, we hypothesised that prediction accuracy with an AS protocol could be different under the contemporary GS system even if the same AS protocol is used.

In the comparison of groups 1 and 2 (Table 2) in our earlier analysis, the accuracy for predicting insignificant prostate cancer was lower in group 1 ($p=0.040$). However, the analysis after excluding patients with CP from group 1 showed a similar prediction accuracy between the two groups ($p=0.146$; Table 4). These findings indicate that the accuracy of the AS protocol for predicting insignificant prostate cancer has been affected by the coexistence of CPs and pure GS 6 tumors in the pre-ISUP2014 era.

In our analysis, 81.8% (9/11) of men with CPs had violated the criteria for insignificant prostate cancer. Seven of the nine patients had harboured at least two reasons among three (GS upgrading, T upstaging, and tumor volume $>0.5 \text{ cm}^3$) for incorrect assignment to AS (Table 5). These findings are in line with a previous study [26] that highlighted an association of the CP with EPE. In their study, EPE was observed in 28.2% of GS 6 cases with CP and in 1.7% of GS 6 cases without CP. Also, the association between CP and the presence of concurrent high-grade carcinoma was demonstrated. Undoubtedly, we believe that the high likelihood of having concurrent EPE or high-grade tumor with CP had led to the inaccuracy of the AS protocol.

Although several recent studies [11,12,27,28] had evaluated the role of mpMRI in reducing the incor-

rect assignment to AS or the cancer detection rate with mpMRI, no study has compared data from the pre-ISUP2014 era with those from the post-ISUP2014 era. Yim et al [28] studied only pre-ISUP2014 data (2006–2013), and Mertan et al [12] analyzed only post-ISUP2014 data (May 2015–September 2015). Luzzago et al [11] (2012–2016 data) and Fan et al [27] (2009–2018 data) enrolled mixed data from both periods.

Regarding the prediction accuracy of Epstein criteria under updated GS system, there were several reports on such issue although most of them analyzed data from pre-2005 *vs.* post-2005 ISUP system. For example, Kryvenko et al [29] studied whether the Epstein criteria could still be valid under the use of updated 2005 GS system, analyzing the patients who underwent RP from 2004 to 2012. The authors demonstrated that the Epstein criteria (either original [22] or modified [29]) maintained its accuracy. As an earlier report, Albertsen et al [30] referred the improved clinical outcome solely as a result of GS reclassification, despite the lack of an actual biologic change (so called Will Rogers phenomenon).

However, our study represents the first description of a comparison of pre-2014 and post-2014 ISUP era data with respect to the accuracy of the AS protocol. Our results suggest that we need to use only contemporary data to analyze the prediction accuracy with AS protocols in future studies. That is to say, we need to use the data only from patients after 2014, or patients whose GS determination was based on 2014 ISUP system, because it is possible that the adoption of 2014 ISUP change did not happen uniformly and instantaneously either depending on institutions. Moreover, such standardization (the use of only post-2014 data) will be important for a more precise determination of the role of mpMRI in AS.

This study has several limitations. First, the number of patients was relatively small. Given the low statistical power of this study, further multicentric studies with more patients are needed to confirm our findings. Second, the retrospective nature also limit this study. Third, the proportions of patients with CPs would be rather variable among numerous previous studies on the AS protocols (in pre-ISUP2014 era); however, this does not diminish our conclusion. The proportion was about 19% (11/57) in the present study. Because it is possible that some old-era studies included a higher proportion of such patients than in the present study,

the results from those studies inevitably have less reliability.

CONCLUSIONS

Our analysis demonstrated that the accuracy of the AS protocol for predicting insignificant prostate cancer has been affected by the coexistence of CPs and pure Gleason 6 tumors in the pre-ISUP2014 era. In future studies, we need to use only contemporary (post-ISUP2014) data when analyzing the prediction accuracy with AS protocols.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: MSC. Data curation: MSC. Formal analysis: SHL, NHC. Investigation: NHC. Resources: NHC, JK, YJ, SHL. Supervision: BIY, SHL. Writing – original draft: MSC. Writing – review & editing: MSC.

Data Sharing Statement

The data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

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