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Comparison of Pathological Outcomes of Active Surveillance Candidates Who Underwent Radical Prostatectomy Using Contemporary Protocols at a High-volume Korean Center

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Objective: We compared contemporary active surveillance protocols based on pathological outcomes in patients who underwent radical prostatectomy.
Methods: We identified the experimental cohort from prostate cancer patients who underwent radical prostatectomy between 2001 and 2011, and who met the inclusion criteria of five published active surveillance protocols, namely Johns Hopkins Medical Institution, University of California at San Francisco, Memorial Sloan-Kettering Cancer Center, University of Miami and Prostate Cancer Research International: Active Surveillance. To compare each protocol, we evaluated the pathological outcomes and calculated the sensitivity, specificity and accuracy for each protocol according to the proportion of organ-confined Gleason $\leq$6 disease.
Results: Overall, 376 patients met the inclusion criteria of the active surveillance protocols with 61, 325, 222, 212 and 206 patients meeting the criteria of the Johns Hopkins Medical Institution, University of California at San Francisco, Memorial Sloan-Kettering Cancer Center, University of Miami and Prostate Cancer Research International: Active Surveillance protocols, respectively. The sensitivity and specificity values of the five protocols, respectively, were 0.199 and 0.882 in Johns Hopkins Medical Institution, 0.855 and 0.124 in University of California at San Francisco, 0.638 and 0.468 in Memorial Sloan-Kettering Cancer Center, 0.599 and 0.479 in University of Miami, and 0.609 and 0.527 in Prostate Cancer Research International: Active Surveillance. In terms of both the sensitivity and specificity, Prostate Cancer Research International: Active Surveillance was the most balanced protocol. In addition, Prostate Cancer Research International: Active Surveillance showed a more accurate performance for favourable pathological outcomes than the others. However, using the area under the curve to compare the discriminative ability of each protocol, there were no statistically significant differences.
Conclusions: The contemporary active surveillance protocols showed similar pathological characteristics in patients who had undergone radical prostatectomy. However, we concluded that the Prostate Cancer Research International: Active Surveillance protocol would be most helpful to Korean populations in choosing candidates for active surveillance considering the balance between sensitivity and specificity and the accuracy of diagnosis.

Key words: prostate cancer – active surveillance – Korean

INTRODUCTION

Radical prostatectomy (RP) is a curative treatment method for localized organ-confined prostate cancer. Therefore, many urologists perform RP in prostate cancer patients diagnosed with clinically localized prostate cancer. Among patients with clinically localized organ-confined prostate cancer who underwent RP, we noted that some have very low-risk prostate cancer with insignificant tumour characteristics (1,2). It is well-known that insignificant prostate cancer tends to have good oncological outcomes (3). Moreover, some urologists suggest that insignificant prostate cancer is the product of overdiagnosis and that RP is overtreatment for these patients (4).

Recently, several studies have reported that active surveillance (AS) is a means of managing low-risk prostate cancer patients and that their own AS protocol is suitable to distinguish low-risk prostate cancer patients with insignificant prostate cancer (5–10). Several published studies have compared the abilities of individual contemporary AS protocols in order to determine which protocol is the most efficient (11–15), but only a few comparisons have been performed in Asian populations. Among these were studies done by Goto et al. (15), who reported on the utility of AS protocols in a Japanese population. However, the small study samples in these studies limited the results. In the present study, we compared the ability of each of five contemporary published AS protocols to predict organ-confined Gleason $\leq$6 prostate cancer by evaluating the pathological outcomes among prostate cancer patients at our institute.

PATIENTS AND METHODS

We reviewed the records of 2108 prostate cancer patients who underwent RP performed by one of four surgeons (K.H.R., B.H.C., S.J.H. and S.C.Y.) between 2001 and 2011 at Yonsei University Hospital, Seoul, Korea. Among them, we excluded 405 patients who received neo-adjuvant treatment and 41 patients who did not undergo prostate magnetic resonance imaging (MRI) for the evaluation of clinical stage. Among the remaining 1662 patients, we identified 376 patients who met the criteria established by the contemporary AS protocols with an available pathological report for the prostate biopsy including all biopsy cores. The clinical stages of all the prostate cancer patients included in this study were determined by prostate MRI.

We stratified patients according to five published AS protocols. These five protocols were from the Johns Hopkins Medical Institution (JHMI) (5), University of California at San Francisco (UCSF) (6), Memorial Sloan-Kettering Cancer Center (MSKCC) (7), University of Miami (UM) (8) and Prostate Cancer Research International: Active Surveillance (PRIAS) (9). The criteria for each AS protocol are shown in Table 1.

Among the study cohort, 170 patients underwent prostate biopsies at our institute. The pathological results of 206 prostate biopsies performed at external hospitals were reviewed by an institutional genitourinary pathologist. A minimum of six cores were examined. Prostate volume (PV) was measured using transrectal ultrasound. However, we calculated the PV by multiplying the prostate weight by 0.85 for the 43 patients lacking PV data (16).

We collected the clinicopathologic outcomes including age, PV, prostate-specific antigen (PSA) at diagnosis, PSA density (PSAD), pre-operative Gleason score, clinical stage, number of prostate biopsy cores, number of positive prostate biopsy cores, single core involvement, post-operative Gleason score, pathological stage, extracapsular extension (ECE), seminal vesicle invasion (SVI), surgical margin status and biochemical recurrence (BCR). We calculated the sensitivity and specificity of each protocol and compared the balance of each protocol according to the sum of the sensitivity and the specificity for organ-confined Gleason $\leq$6 prostate cancer. And we also compared the diagnostic accuracy for organ-confined Gleason $\leq$6 prostate cancer.

To compare the pathological outcomes of each protocol, we used Fisher's exact test. The actual risk of BCR was calculated using the Kaplan–Meier method. To compare the discriminative ability of each protocol, the area under the receiver operating characteristics curve (AUC) was calculated. All statistical analyses were performed using the SAS statistical package (Version 9.1; SAS Institute, Cary, NC, USA). A P value of $\leq$0.05 was considered statistically significant.

Table 1. Active surveillance protocols in recently published literature

Protocol (principal investigator)	Gleason score	Clinical stage	PSA (ng/ml)	PSAD	No. of positive cores	Single core involvement (%)
JHMI	$\leq$6, no pattern 4 or 5	T1c	—	$\leq$0.15	$\leq$2	$\leq$50
UCSF	$\leq$6, no pattern 4 or 5	T1c-T2	$\leq$10	—	$\leq$33 (of at least 6)	$\leq$50
MSKCC	$\leq$6	T1c-T2a	$\leq$10	—	$\leq$3	$\leq$50
UM	$\leq$6	T1c-T2	$\leq$15	—	$\leq$2	$\leq$20
PRIAS	$\leq$6	T1c-T2	$\leq$10	$\leq$0.2	$\leq$2	—

JHMI, Johns Hopkins Medical Institution; UCSF, University of California at San Francisco; MSKCC, Memorial Sloan-Kettering Cancer Center; UM, University of Miami; PRIAS, Prostate Cancer Research International: Active Surveillance.

Table 2. Baseline characteristics of the study cohort

No. of patients	376
Age	63.7 ± 7.17
Prostate volume	39.9 ± 17.8
PSA	6.26 ± 2.43
PSAD (mean)	0.18
Clinical stage	
cT1c	144 (38.3%)
cT2a/b	179 (47.6%)
cT2c	53 (14.1%)
No. of positive biopsy cores	
1	202 (53.7%)
2	105 (27.9%)
3	50 (13.3%)
≥4	19 (5.1%)
Average percentage core involvement	18.1%
Post-operative Gleason score	
≤6	234 (62.3%)
7	134 (35.6%)
8–10	8 (2.1%)
Primary Gleason score 4	46 (12.2)
Any Gleason score 5	5 (1.3)
Pathological stage	
pT2	314 (83.5%)
pT3	62 (16.5%)
Extracapsular extension	59 (15.7%)
Seminal vesicle invasion	3 (0.8%)
Positive surgical margin	84 (22.3%)
Upstaging (pT3)	62 (16.5%)
Upgrading (post-operative Gleason score 7–10)	142 (37.7%)
Organ-confined Gleason score ≤6 disease	207 (55.1%)
Unfavourable disease (ECE, SVI, Gleason score 8–10)	67 (17.8%)

PSA, prostate-specific antigen; PSAD, PSA density; ECE, extracapsular extension; SVI, seminal vesicle invasion.

RESULTS

The baseline characteristics of patients who met the criteria of each protocol are shown in Table 2. A total of 376 AS candidates underwent RP with 61, 325, 222, 212 and 206 patients meeting the JHMI, UCSF, MSKCC, UM and PRIAS criteria, respectively. The mean age was 63.7 ± 7.17 years, the mean PSA was 6.26 ng/ml, and the mean PSAD was 0.18. A total of 202 (53.7%) patients had one positive core. The percentage of patients having single core involvement was 18.1%.

In evaluating the pathological specimens, 234 (62.3%) patients were found to have a post-operative Gleason score of ≤6 and 8 (2.1%) patients had post-operative Gleason scores of 8–10. Gleason upgrading (post-operative Gleason scores 7–10) was observed in 142 (37.7%) patients. A primary Gleason score of 4 was noted in 46 (12.2%) patients, and 5 (1.3%) patients had a Gleason score of 5. Pathological stage T2 was described in 314 (83.5%) patients, and T3 (upstaging) was observed in 62 (16.5%) patients. ECE occurred in 59 (15.7%) patients, and SVI occurred in 3 (0.8%) patients. Organ-confined Gleason ≤6 prostate cancer was found in 207 (55.1%) patients, and 67 (17.8%) patients were characterized by unfavourable disease features (ECE and/or SVI and/or post-operative Gleason scores 8–10).

Table 3 shows the pathological outcomes of each protocol. There were no statistical differences in the distribution of post-operative Gleason scores, pathological stages, post-operative upgrading, organ-confined Gleason ≤6 disease, unfavourable disease features and BCR rate. A log-rank test of the Kaplan–Meier survival curves demonstrated no significant difference in overall BCR rate across each protocol (Fig. 1, log rank $P = 0.754$). However, the JHMI protocol showed the lowest sensitivity, and the UCSF protocol showed the lowest specificity. The PRIAS protocol had the best balance between sensitivity and specificity among the five AS protocols. In addition, the PRIAS protocol had the best diagnostic accuracy for organ-confined Gleason ≤6 prostate cancer (Table 4).

Comparing the area under the curve for the discriminative ability of each protocol, the JHMI protocol showed a lower AUC (57.7%) compared with the other protocols. However, there was no statistically significant difference between the AS protocols (Table 5 and Fig. 2).

DISCUSSION

One of the recent issues related to prostate cancer is over-diagnosis and overtreatment. Because of PSA screening, the increasing incidence of prostate cancer is an ongoing phenomenon in Korea and the rest of Asia as well. The increased number of diagnoses of clinically localized prostate cancer is remarkable in comparison with the number in past decades in Korea and RP is the main treatment choice of these patients in Korea (17). In observing the natural course of prostate cancer, low-risk prostate cancer patients have better oncological outcomes than other risk groups. It is obvious that insignificant prostate cancer after RP suggests over-diagnosis and overtreatment. To reduce overtreatment of these patients, several investigators have developed their own AS programme.

Recently, long-term follow-up data with AS were reported from several institutes. Klotz et al. (18) reported that the 10-year survival rate for prostate cancer was 97.2% in their AS group. They concluded that low-risk prostate cancer has a low mortality rate; however, more precise identification of AS candidates is needed. Holmström et al. (19) reported that there were no statistical differences between the AS cohort

Table 3. Pathological outcomes of different active surveillance protocols

	JHMI	UCSF	MSKCC	UM	PRIAS	*P* value
No. of patients	61	325	222	212	206	
Post-operative Gleason score						
≤6	43 (70.5%)	202 (62.2%)	147 (66.2%)	143 (67.4%)	138 (67.0%)	0.787
7	16 (26.2%)	117 (36.0%)	71 (31.9%)	64 (30.2%)	63 (30.6%)	
8–10	2 (3.3%)	6 (1.8%)	4 (1.9%)	5 (2.4%)	5 (2.4%)	
Pathological stage						
pT2	56 (91.8%)	268 (82.5%)	189 (85.1%)	177 (83.5%)	179 (86.9%)	0.111
pT3 (upstaging)	5 (8.2%)	57 (17.5%)	33 (14.9%)	35 (16.5%)	21 (10.2%)	
Upgrading (post-operative Gleason score 7–10)	18 (29.5%)	123 (37.8%)	75 (33.8%)	69 (32.5%)	68 (33.0%)	0.592
Organ-confined Gleason ≤6 disease	41 (67.2%)	177 (54.5%)	132 (59.5%)	124 (58.5%)	126 (61.2%)	0.218
Unfavourable disease[a]	7 (11.5%)	59 (18.2%)	36 (16.2%)	39 (18.3%)	29 (14.0%)	0.548
Biochemical recurrence rate	2 (3.3%)	24 (7.4%)	13 (5.9%)	16 (7.5%)	12 (5.8%)	0.763

[a]Extracapsular extension and/or seminal vesicle invasion and/or Gleason scores 8–10.

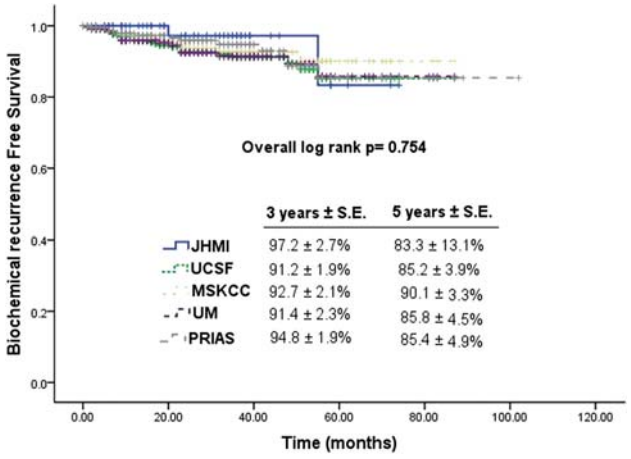

Figure 1. Comparison of Kaplan–Meier biochemical recurrence-free survival curves after radical prostatectomy across the active surveillance protocols (JHMI, Johns Hopkins Medical Institution; UCSF, University of California at San Francisco; MSKCC, Memorial Sloan-Kettering Cancer Center; UM, University of Miami; PRIAS, Prostate Cancer Research International: Active Surveillance).

Table 4. Comparison of the diagnostic accuracy of the active surveillance protocols for organ-confined Gleason score ≤6 disease

	JHMI	UCSF	MSKCC	UM	PRIAS
Sensitivity	0.199	0.855	0.638	0.599	0.609
Specificity	0.882	0.124	0.468	0.479	0.527
Positive predictive value	0.672	0.544	0.594	0.584	0.612
Negative predictive value	0.190	0.156	0.201	0.170	0.224
Accuracy	0.505	0.525	0.558	0.546	0.569

Table 5. Comparison of receiver operating characteristic curves of the active surveillance protocols for organ-confined Gleason score ≤6 disease

	P value					
	AUC	95% CI	JHMI	UCSF	MSKCC	UM
JHMI	0.577	0.426–0.728	—	—	—	—
UCSF	0.621	0.590–0.652	0.600	—	—	—
MSKCC	0.612	0.573–0.651	0.687	0.856	—	—
UM	0.613	0.573–03653	0.681	0.872	0.987	—
PRIAS	0.615	0.574–0.656	0.665	0.907	0.957	0.970

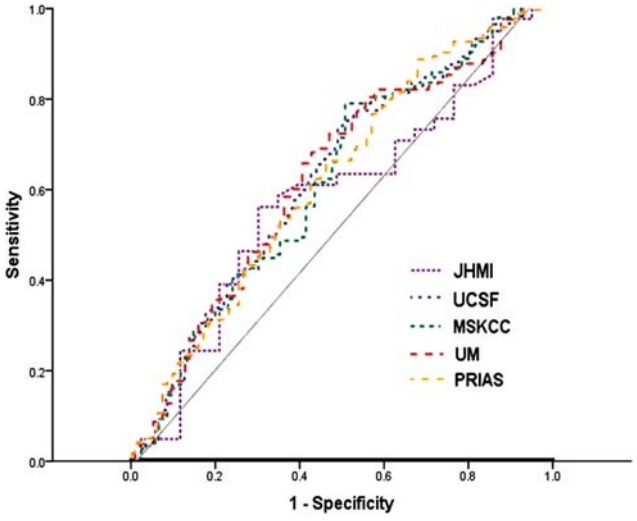

Figure 2. Comparison of receiver operating characteristic curves of the active surveillance protocols for organ-confined Gleason 6 disease.

and the low-risk prostate cancer cohort of patients who were treated with RP and radiotherapy during a 10-year follow-up period (19). Recently, Suardi et al. (20) concluded that an AS programme is significantly better for managing prostate cancer patients younger than 70 years. Drawing from these studies, we suggest that AS is a suitable option for reducing overtreatment in low-risk prostate cancer patients.

In the present study, we compared five contemporary AS protocols from the following institutions: the JHMI (5), UCSF (6), MSKCC (7), UM (8) and PRIAS (9). Another AS protocol used in an Asian cohort also exists; it was developed by the KaKehi et al. (10) research team in Japan. However, this AS protocol includes intermediate-risk prostate cancer patients with a PSA level of <20 ng/ml as AS candidates. Therefore, despite the fact that this AS protocol was developed in an Asian population, we excluded it from the present study because we chose to focus specifically on low-risk prostate cancer patients.

When comparing the characteristics of each protocol's criteria, it is evident that the JHMI protocol is most stringent. The JHMI protocol is limited to patients with clinical stage T1c disease and PSAD ≤ 0.15 ng/ml. In contrast, the UCSF protocol has the most lenient inclusion criteria among the protocols. This protocol has no limitations regarding the number of positive cores. According to their criteria, all patients with 33% positive cores among any number of total cores could be AS candidates. These conditions were also applied to the present study. We identified only 61 patients (16.2% of 376) who fulfilled the JHMI criteria, while 325 (86.4% of 376) fulfilled the UCSF criteria. The PRIAS, MSKCC and UM protocols had similar numbers of AS candidates among the prostate cancer patients who underwent RP at our institute despite slight differences in their individual criteria.

Although there are some differences in the details of each protocol, the overarching aims of all AS protocols are similar: to identify prostate cancer patients with indolent tumours and to reduce aggressive treatment in these patients. When we compared the pathological outcomes of AS candidates who underwent RP according to the criteria of different AS protocols, we found that all the five AS protocols fulfilled these aims sufficiently. The discriminative performance of each protocol and the BCR survival rate of AS candidates were not statistically different (Figs. 1 and 2). We determined that selection of AS candidates based on the JHMI protocol resulted in the lowest frequencies of upstaging, upgrading and unfavourable disease. The JHMI protocol showed the best ability to identify organ-confined prostate cancer with a Gleason score of ≤ 6 (Table 3). However, only 61 men benefitted from the programme because of the stringent JHMI criteria. When we examined the pathological outcomes of the 315 patients in other AS protocols, we found that 165 (52%) had organ-confined Gleason ≤ 6 prostate cancer, while 60 (19%) had unfavourable disease features with a Gleason score of 8–10 and/or ECE and/or SVI. This means that these 165 men lost the opportunity to undergo AS, and the disease would have progressed in 60 of the patients with unfavourable disease had they undergone AS. We thought that the losses outweighed the gains in the JHMI protocol when considering the aim of the AS protocol. By contrast, the UCSF protocol showed the opposite results compared with the JHMI protocol. Because of the more lenient inclusion criteria, 325 men could have been AS candidates based on the UCSF protocol. However, the pathological outcomes were generally not good in comparison with the results from the other four AS protocols. Even though more prostate cancer patients had the chance to use the AS program using the UCSF protocol, urologists would lose the chance for proper timing and decision-making for patients with unfavorable disease if they were included in the UCSF protocol. In other words, the JHMI protocol and the UCSF protocol did not perform well with regard to the balance between the sensitivity and the specificity (Table 4).

The remaining three AS protocols resulted in the selection of a similar number of AS candidates and the balance between the sensitivity and specificity of the protocols were also quite similar. In terms of pathological outcomes and the balance between sensitivity and specificity among these three AS protocols, the PRIAS protocol performed the best in selecting AS candidates. In addition, the PRIAS protocol had the highest diagnostic accuracy for organ-confined Gleason ≤ 6 prostate cancer. This result is similar to that from the evaluation of a Japanese cohort (15).

On the basis of our findings, we consider the PRIAS protocol the most balanced and accurate AS protocol for Korean populations because of the background of its development. AS protocols from JHMI, UCSF, MSKCC and UM were generated on the basis of the data from the individual institutions. However, the PRIAS protocol was developed for an international prospective study of AS, although it originated from the Randomized Study of Screening for Prostate Cancer (ERSPC) and was initiated in the Erasmus MC in the Netherlands (21). This protocol's criteria were developed with consideration for cultural and genetic background. The specific difference from other AS protocols is that the PRIAS does not include single core involvement data. Van den Bergh et al. (21) explained that the single core involvement information was excluded because the use of each specific core in determining the percentage of cancer involvement is not a currently standard procedure at all pathology centrer. This decision rendered the unintended and coincidental result that use of the PRIAS protocol has better outcomes than the other protocols. Because there is no consensus on the predictability of the prostate biopsy profile using Western cohorts, the question remains as to whether or not it could be applied to Asian cohorts.

Recently, Choi et al. reported the predictors for insignificant prostate cancer after RP in a Korean sample (22). They reviewed the pathological outcomes of 1471 men who were treated at multiple institutions in Korea. They concluded that insignificant prostate cancer in Koreans had the following characteristics: mean preoperative PSA, 5.3 ng/ml; mean

Table 6. Predictive variables between significant and insignificant prostate cancers in Korean patients

Variables	Significant prostate cancer	Insignificant prostate cancer[a]	*P* value
Mean PSA	12.7 ± 15.7	5.3 ± 6.9	<0.001
PSAD	0.42 ± 0.41	0.21 ± 0.11	<0.001
Mean no. of positive biopsy core	3.9 ± 2.6	1.6 ± 1.5	<0.001
Average percentage core involvement	0.39 ± 0.25	0.13 ± 0.12	<0.001
Maximum % tumour in any core	47.5 ± 31.3	16.8 ± 16.1	<0.001

[a]A total tumour volume of <0.5cc with organ-confined Gleason ≤6 prostate cancer.
This table was modified and cited with permission from Chung et al. (22).

PSAD, 0.21; mean number of positive cores, 1.6; average percentage of core involvement, 0.13% and maximum percentage of any single core, 16.8% (Table 6). These conditions are consistent with the PRIAS protocol. In contrast, the criteria for the MSKCC protocol and the UM protocol measured similar characteristics, but evaluated significant prostate cancer rather than insignificant prostate cancer in Korean populations. Therefore, these studies support the argument that the PRIAS protocol is an appropriate protocol for Korean patients.

It is possible to develop a novel AS protocol for Korean populations to predict insignificant prostate cancer using a Korean database. However, this is beyond the scope of the present study. Nevertheless, we believe that a more accurate and balanced AS protocol for Asian populations is needed. We found that the proportion of patients with organ-confined Gleason ≤6 prostate cancer is lower in Korean populations than in Western populations (11). There is a difference in incidence of about 13–16% between populations according to the results of Korean and Western studies using each of the AS protocols. We found this phenomenon not only in the present study, but also in another study of a Korean cohort (23,24). Despite the fact that the authors used the JHMI protocol (Epstein criteria), which has the most stringent characteristics, they indicated that Korean patients seem to have a greater incidence of prostate cancer with unfavourable pathological features than do Western patients. On the basis of this assertion, we debated whether or not a comparison of the ability of each published AS protocol has significant meaning. This is because the performance of the AS protocols generally differs between Western and Asian cohorts. However, considering that an AS protocol optimized for Asian cohorts does not yet exist, a validation of the existing AS protocols would be important both for urologists and for patients because AS will soon become one of the main treatment choices in Asian populations (25).

A main limitation of the present study is that we simply examined the pathological outcomes in prostate cancer patients who underwent RP. Recently, many studies have reported the oncological outcomes of the AS programme in real practice and the pathological outcomes of prostate cancer patients who underwent RP after AS because of suspicious disease progression. Therefore, some readers could regard our findings as outdated. However, considering the fact that there have not yet been studies comparing published AS protocols using Asian cohorts, our results might be helpful in guiding urologists' selection of the proper AS protocol to use for low-risk prostate cancer patients, particularly AS candidates.

In conclusion, the present study shows that RP specimens evaluated according to contemporary AS protocols have quite similar pathological characteristics. Nevertheless, we conclude that among the five AS protocols studied, the PRIAS protocol would be most helpful in choosing the appropriate patients for AS when taking into consideration the balance between sensitivity and specificity, diagnostic accuracy and characteristics of Korean patients with insignificant prostate cancer. We believe that the development of an optimized AS protocol for Asian populations is the next logical step moving forward.

Conflict of interest statement

None declared.

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