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Original Article

Is prostate specific antigen (PSA) density necessary in selecting prostate cancer patients for active surveillance and what should be the cutoff in the Asian population?

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ABSTRACT

Background: To investigate the role of Prostate Specific Antigen density (PSAD) in selecting prostate cancer patients for active surveillance (AS) and to determine a cutoff PSAD in identifying adverse pathological outcomes.

Methods: Data from 287 patients who underwent radical prostatectomy for prostate cancer were retrospectively reviewed. Six different AS protocols, the University of Toronto; Royal Marsden; John Hopkins; University of California San Francisco (UCSF); Memorial Sloan Kettering Cancer Center (MSKCC) and Prostate Cancer Research International: Active Surveillance (PRIAS), were applied to the cohort. Pre-operative demographics and pathological outcomes were analysed. Statistical analyses on the predictive factors of adverse pathological outcomes and significance of PSAD were performed. A cutoff PSAD with best balance between sensitivity and specificity in identifying adverse pathological outcome was determined.

Results: PSAD predicted adverse pathological outcomes better than Prostate Specific Antigen (PSA) level alone. The PSAD was significantly lower (0.12–0.13 ng/dl/ml) in protocols including PSAD (the John Hopkins and PRIAS) compared with the other four protocols not including PSAD as a selection criteria (0.21–0.25 ng/dl/dl, $P = 0.00$). PSAD predicted adverse pathological outcomes in all protocols not incorporating PSAD as an inclusion criteria ($P = 0.00$–0.02). By the receiver operator characteristics curve analysis, it was found that a PSAD level of 0.19 ng/ml/ml had the best balance between sensitivity and specificity in predicting pathological adverse disease (Area under curve = 0.63, $P = 0.004$).

Conclusion: PSAD is necessary in selecting prostate cancer patients for active surveillance. It predicts adverse pathological outcomes in patients eligible for active surveillance better than PSA level alone. A PSAD cutoff at 0.19 ng/ml/ml has the best balance between sensitivity and specificity in predicting pathological adverse disease. We recommend using AS protocol incorporating PSAD as a selection criteria (in particular the PRIAS protocol with a cutoff PSAD at 0.2 ng/ml/ml) when recruiting prostate cancer patients for AS.

1. Introduction

In the era of PSA screening, over diagnosis of low-risk prostate cancer is not uncommon.[1] Active surveillance (AS) is an established treatment for low-risk prostate cancer. With AS, radical treatments were delayed until occurrence of clinical, biochemical, or histological progression.[2–5] In this way, morbidities associated with radical prostatectomy or radiotherapy can be avoided.[6–9] Different AS protocols were proposed, and the heterogeneity among them is wide. It was reported that pathological nonorgan confined disease and upgrade of Gleason score were present in 8.5%–23.8% and 13.1%–21.8% of patients eligible for different AS criteria.[10]

Most AS protocols select patients for surveillance base on PSA level, biopsy Gleason score, clinical T staging, number of positive biopsy core, and percentage of core involvement.[11–14] PSA density (PSAD) was believed to be higher in patients with more aggressive

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prostate cancer.[15,16] In addition, it was shown that PSAD was an independent predictor of Gleason score upgrade upon radical prostatectomy.[17] It also predicted Gleason upgrade during repeat biopsies better than PSA.[18] With the above peripheral evidence, PSAD may have an implication in the inclusion criteria for AS.

Despite the potential role of PSAD in selecting low-risk prostate cancer for AS, not all AS schemes include PSAD as a selection criteria. The Johns Hopkins criteria and Prostate Cancer Research International: Active Surveillance (PRIAS) protocol are two commonly used AS protocols that include PSAD in their inclusion criteria.[19–21] Literature comparing AS protocols with and without PSAD as inclusion criteria and information on the role of PSAD in AS is lacking. In our current study, we aim to evaluate the predictive factors of adverse pathological outcomes in different AS protocols, examine the significance of PSAD, and determine a cutoff PSAD with best balance between sensitivity and specificity in identifying adverse pathological outcomes from an Asian cohort.

2. Material and methods

Two hundred eighty-seven patients underwent radical prostatectomy from 1998 to 2012 in our institution. Digital rectal examination for clinical T staging, serum PSA level, and transrectal ultrasound guided prostate biopsy were performed in all patients. Transrectal ultrasound guided biopsy and radical prostatectomy specimens were assessed by specialist pathologists. Data including patient demographics, clinical T stage, PSA level, number of positive biopsy cores, transrectal ultrasound measured prostate volume, biopsy Gleason score, PSAD, and radical prostatectomy specimen pathologies were retrieved.

Eligibility of each patient to be recruited in AS according to six different AS protocols were retrospectively reviewed (Table 1). The AS criteria from the University of Toronto,[11] Royal Marsden,[12] John Hopkins,[19,20] University of California San Francisco (UCSF),[13] Memorial Sloan Kettering Cancer Center (MSKCC)[14] and PRIAS[21] were included. The differences between clinical T staging, number of positive cores in biopsy, Gleason score, PSA level, and PSADs among different protocols were analyzed. Patients in the four protocols not including PSAD were further stratified according to the presence of pathological adverse disease, and the differences in clinical T staging, number of positive cores in biopsy, Gleason score, PSA level, and PSADs between the two groups were compared. Finally, receiver operator characteristics (ROC) curve analysis was performed. A cutoff PSAD with the best balance between sensitivity and specificity in predicting pathological adverse disease was determined by the coordination points of the ROC curve.

Statistical analyses were performed by SPSS, version 20. Independent sample *t* test and Pearson Chi-square test were used for continuous and categorical variables, respectively, predictive factors for adverse pathology was determined by logistic regression analysis, and coordination points of ROC curve analysis was used to determine the cutoff PSAD. Statistical significance was defined as P value ≤ 0.05.

Table 2
Basic demographics of patients.

Demographics	Mean (Range)
N	287
Age, years	66 (48–79)
PSA, ng/ml	10 (1–68)
Number of positive cores	3 (1–10)
Biopsy Gleason sum	6 (6–10)
Gleason 3 + 3	N = 229 (79%)
Gleason 3 + 4	N = 26 (9%)
Gleason 4 + 3	N = 16 (6%)
Gleason sum 8–10	N = 16 (6%)
Clinical T stage:	Number (percentage)
T1a	3 (1.0%)
T1b	0 (0.0%)
T1c	198 (69.0%)
T2a	68 (23.7%)
T2b	6 (2.1%)
T2c	10 (3.5%)
T3a	2 (0.7%)

3. Results

A total of 287 patients were included in the cohort. One hundred fifty-two patients fulfilled the University of Toronto criteria; 165 patients fulfilled the Royal Marsden criteria; 30 patients fulfilled the John Hopkins criteria; 90 patients fulfilled the UCSF criteria; 91 patients fulfilled the MSKCC criteria; and 63 patients fulfilled the PRIAS criteria. Table 2 summarized the basic demographics of the cohort. Table 3 summarized the demographics and pathological outcomes of patients after stratifying into different AS protocols.

The difference in preoperative characteristics and pathological outcomes between the six AS protocols was compared (Table 3). The PSADs of 0.21–0.25 ng/ml/ml in the four protocols not selecting patients by PSAD (University of Toronto, Royal Marsden, UCSF, MSKCC) were higher than the PSADs of 0.12–0.13 mg/ml/ml in both protocols including PSAD in their inclusion criteria (John Hopkins and PRIAS) ($P = 0.00$).

Next, we determined if higher PSAD could predict adverse pathological outcomes. Each of the four protocols not selecting patients by PSAD (University of Toronto, Royal Marsden, UCSF, MSKCC) were further divided into two groups depending on the presence of adverse pathological outcomes during radical prostatectomies. Adverse pathological outcome was defined as any upgrade in Gleason sum or presence of pathological T3 disease (extracapsular extension or seminal vesicle invasion) in the prostatectomy specimens. Table 4 showed the comparison of PSA level, PSADs, Gleason score, and number of positive biopsy cores between the groups by logistic regression. It was found that PSAD significantly predicted adverse pathological outcomes in all the four protocols not incorporating PSAD as an inclusion criteria ($P = 0.00–0.02$). PSA predicted adverse pathological outcomes only in the University of Toronto and Royal Marsden protocol ($P = 0.01–0.04$) but not in the UCSF and MSKCC protocols. Therefore, PSAD is a better predictive tool than PSA level.

Table 1
Inclusion criteria of six active surveillance protocols.

Parameters	University of Toronto	Royal Marsden	John Hopkins	UCSF	MSKCC	PRIAS
PSA (ng/ml)	≦10	≦15	/	≦10	≦10	≦10
PSA density (ng/ml/ml)	/	/	≦0.15	/	/	<0.2
Clinical T stage	/	T1/T2a	T1	T1/T2	T1/T2	T1/T2
Gleason score	≦3 + 3	≦3 + 4	≦6	≦6	≦6	≦6
Positive biopsies	/	≦50%	≦2	<33% of all biopsies	≦3	≦2
Percentage of core involvement	/	/	≦50%	/	≦50%	/

UCSF, University of California San Francisco; MSKCC, Memorial Sloan Kettering Cancer Center; PRIAS, Prostate Cancer Research International: Active Surveillance.

Table 3
Demographics of patients stratified according to six different AS protocols.

Demographics	University of Toronto	Royal Marsden	John Hopkins	UCSF	MSKCC	PRIAS
N	152	165	30	90	91	63
Age, years (mean)	48–79 (65)	48–79 (66)	50–75 (64)	48–79 (65)	48–79 (66)	48–79 (65)
PSA, ng/ml (mean)	1.5–10 (6.8) versus Royal Marsden $P = 0.002$ versus John Hopkins $P = 0.001$ versus PRIAS $P = 0.000$	2.8–15 (7.7) versus University of Toronto $P = 0.002$ versus John Hopkins $P = 0.000$ versus UCSF $P = 0.000$ versus MSKCC $P = 0.001$ versus PRIAS $P = 0.000$	2.8–8.6 (5.3) versus University of Toronto $P = 0.001$ versus Royal Marsden $P = 0.000$	2.8–10 (6.5) versus Royal Marsden $P = 0.000$	2.8–10 (6.5) versus Royal Marsden $P = 0.001$	2.8–10 (5.6) versus University of Toronto $P = 0.000$ versus Royal Marsden $P = 0.000$
Prostate volume, ml (mean)	12–97 (35)	11–97 (36)	23–97 (46)	13–97 (36)	13–97 (36)	19–97 (44)
PSA density, ng/ml/ml(mean)	**0.04–0.83 (0.22) versus John Hopkins $P = 0.00$ versus PRIAS $P = 0.00$**	**0.04–1.00 (0.25) versus John Hopkins $P = 0.00$ versus PRIAS $P = 0.00$**	**0.05–0.14 (0.12) versus University of Toronto $P = 0.00$ versus Royal Marsden $P = 0.00$ versus UCSF $P = 0.00$ versus MSKCC $P = 0.00$**	**0.05–0.64 (0.21) versus John Hopkins $P = 0.00$ versus PRIAS $P = 0.00$**	**0.05–0.64 (0.21) versus John Hopkins $P = 0.00$ versus PRIAS $P = 0.00$**	**0.04–0.2 (0.13) versus University of Toronto $P = 0.00$ versus Royal Marsden $P = 0.00$ versus UCSF $P = 0.00$ versus MSKCC $P = 0.00$**
Number of positive core (mean)	1–8 (2) versus John Hopkins $P = 0.008$ versus UCSF $P = 0.001$ versus MSKCC $P = 0.000$ versus PRIAS $P = 0.000$	1–6 (2) versus PRIAS $P = 0.000$	1–2 (1) versus University of Toronto $P = 0.008$	1–4 (2) versus University of Toronto $P = 0.001$	1–3 (2) versus University of Toronto $P = 0.000$	1–2 (1) versus University of Toronto $P = 0.000$ versus Royal Marsden $P = 0.000$
Mean Gleason sum	6	6	6	6	6	6
Clinical T stage						
T1a	1 (0.7%)	1 (0.6%)	0	1 (1.1%)	1 (1.1%)	1 (1.6%)
T1b	0	0	0	0	0	0
T1c	123 (80.9%)	134 (81.2%)	30 (100%)	77 (85.6%)	78 (85.7%)	52 (82.5%)
T2a	25 (16.4%)	30 (18.2%)	0	12 (13.3%)	12 (13.2%)	10 (15.9%)
T2b	0	0	0	0	0	0
T2c	3 (2.0%)	0	0	0	0	0
T3a	0	0	0	0	0	0
Pathological outcome						
Upgrade of Gleason score, N (%)	47 (31%)	58 (35%)	8 (27%)	26 (29%)	27 (30%)	13 (21%)
Pathological T3 disease, N (%)	29 (19%)	26 (16%)	1 (3%)	15 (17%)	15 (17%)	5 (8%)

AS, active surveillance; MSKCC, Memorial Sloan Kettering Cancer Center; PRIAS, Prostate Cancer Research International: Active Surveillance; UCSF, University of California San Francisco.
$P > 0.05$ were not shown.
The bold values signifies statistical significant results.

Table 4
Predictive factors of adverse pathological outcomes by logistic regression.

Adverse pathological outcomes	University of Toronto			Royal Marsden			UCSF			MSKCC		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
PSA (ng/ml)	7.20	6.45	***0.04***	8.39	7.21	***0.01***	6.96	6.18	0.06	6.95	6.25	0.09
Number of positive cores	2.24	2.13	0.68	1.91	1.97	0.77	1.53	1.58	0.78	1.51	1.56	0.78
Biopsy Gleason sum	6	6	/	6.94	6.04	0.22	6	6	/	6	6	/
PSA density (ng/ml/ml)	0.26	0.20	***0.00***	0.29	0.22	***0.01***	0.25	*0.19*	***0.02***	0.24	0.19	***0.02***

UCSF, University of California San Francisco; MSKCC, Memorial Sloan Kettering Cancer Center.
Adverse pathological outcomes: pathological T3 disease or any Gleason upgrade in radical prostatectomies.
The bold and italics values signifies statistical significant results.

In the last part of our study, ROC curve was plotted (Fig. 1). The area under curve of PSAD in predicting adverse pathological outcome was 0.63 ($P = 0.004$). A cutoff PSAD with the best balance between sensitivity and specificity in identifying patients with adverse pathological outcome was derived by the coordination points of the curve. According to the coordinates of the curve, a PSAD cutoff at 0.19 ng/ml/ml was found (sensitivity: 72%, specificity: 52%).

4. Discussion

In the contemporary era, the role of AS in management of low-risk prostate cancer was well established.[2–5] Different AS protocols were proposed, and most of them select patients base on PSA level, biopsy Gleason score, clinical T staging, number of positive biopsy core, and percentage of core involvement.[11–14] PSAD was believed to be predictive of aggressive prostate cancer.[15,16] It was an independent predictor of Gleason score upgrade in radical prostatectomies and repeat prostate biopsies.[17,18] With the above evidence, PSAD may have a role in identifying low-risk disease for AS. However, the role and implication of PSAD in AS selection is not well studied. PSAD is included in two of the commonly used AS protocols only.[19–21] In addition, the PSAD cutoff level are different between different protocols.[19–21] Currently, there is no consensus regarding the role of PSAD in AS and the optimal PSAD cutoff level, especially in the Asian population. In our study, we provided insights into these issues.

In this study, data from patients with low-risk prostate cancer who were eligible for AS but underwent radical prostatectomies were analyzed. It was found that PSAD was significantly lower in protocols selecting patients according to PSAD compared with protocols not considering PSAD. In addition, we demonstrated the mean PSAD was significantly higher in patients with adverse pathological outcome in all protocols not taking PSAD as an inclusion criteria. Finally, we determined a cutoff PSAD at 0.19 ng/ml/ml with the best balance between sensitivity and specificity in predicting pathological adverse disease.

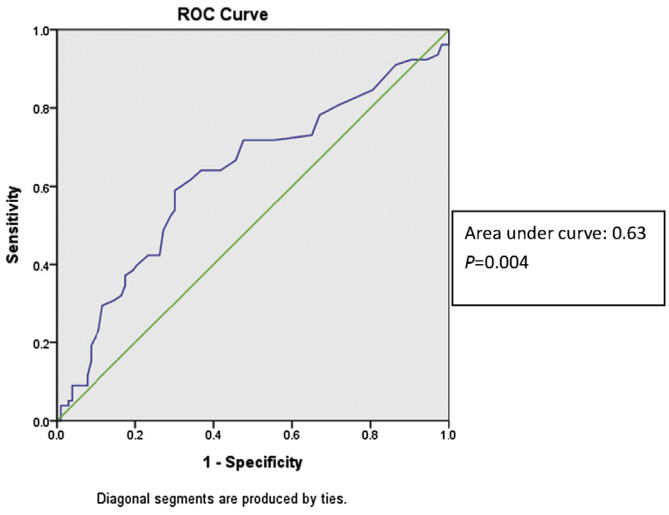

Figure 1. Receiver operator characteristic curve of PSAD. PSAD, PSA density; ROC, Receiver operator characteristic.

In our cohort, 10%–57% of the patients were eligible for AS according to different selection criteria (Table 3). Similarly, Iremashvili et al and El Hajj et al demonstrated that eligibility for different AS protocols varies from 16% to 63% and 28% to 69%.[22,23] Altogether, these suggested that despite the same aim to select low-risk patients for AS, there is a large variation in stringency between different protocols. It was reported that the John Hopkins and PRIAS criteria (the only protocols that take PSAD into account in their selection criteria) have the lowest incidence of adverse pathological outcome among different AS protocols.[24] Such results provided clues that PSAD may have an implication in identifying low-risk prostate cancer in AS.

Secondly, we looked into the difference in selection criteria in all six AS protocols (Table 3). When PSAD was assessed, it was significantly lower in the protocols including PSAD as selection criteria (John Hopkins and PRIAS criteria) compared with all other protocols that do not take PSAD into account. Besides echoing our earlier suggestion that there is a wide range of variation in stringency between different AS protocols, these provided another evidence that including PSAD in AS could lead to a more selective and stringent protocol.

Next, patients in the protocols not including PSAD as inclusion criteria were stratified into two groups according to the presence or absence of adverse pathological outcomes. It was found that PSAD was a predictor of adverse pathological outcomes in all protocols and was better than PSA level alone for the prediction of adverse pathological outcomes (Table 4). Similarly, Ha et al concluded that among patients with low-risk prostate cancer who underwent radical prostatectomy, PSAD was a predictor of advanced disease at the time of surgery.[25] However, only three AS protocols were examined in their study, and herein, we provided additional information as more AS protocols were studied in our current study.

Since different PSADs were adopted by different AS protocols, objective determination of an optimal PSAD is necessary. A cutoff PSAD at 0.19 ng/ml/ml with the best balance between sensitivity and specificity in identifying adverse pathological outcome was derived by the coordination points of the receiver operator characteristic curve. A PSAD of 0.085 ng/ml/ml was proposed by Ha et al.[24] This level is much lower than a PSAD of 0.15 ng/ml/ml and 0.2 ng/ml/ml used in the John Hopkins and PRIAS criteria, respectively. This can be explained by the fact that this cutoff was determined among highly selected population eligible for more stringent AS protocols using PSAD as selection criteria. In our study, PSAD of 0.19 ng/ml/ml was determined based on a population

eligible for six different AS protocols regardless of PSAD as selection criteria. Therefore, our cutoff PSAD is more suitable to be applied to general prostate cancer patients instead of a preselected very low-risk population.

In conclusion, PSAD significantly predicted adverse pathological outcomes in patients eligible for active surveillance. Therefore, PSAD is essential in selecting prostate cancer patients for AS. A PSAD cutoff at 0.19 ng/ml/ml had the best balance between sensitivity and specificity in predicting pathological adverse disease in the Asian population. We recommend using AS protocol incorporating PSAD as a selection criteria when recruiting prostate cancer patients for AS. In particular, the PRIAS protocol with a cutoff PSAD at 0.2 ng/ml/ml (closest to 0.19 ng/ml/ml) is recommended.

There are some limitations in our study. The sample size of our cohort is relatively small because of the low incidence of prostate cancer in our population. In addition, insignificant disease in terms of tumor volume in radical prostatectomy specimen was not included. Furthermore, the area under curve for PSAD in predicting adverse pathological outcome is only 0.63, this could be a shortcoming when incorporating PSAD in AS. Finally, the retrospective nature of the study is another limitation.

Conflicts of interest

All authors have disclosed no financial support and no conflicts of interest in this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.prnil.2018.03.002.

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