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The presence of prostate-specific antigen checked more than 1 year before diagnostic biopsy is an independent prognostic factor in patients undergoing radical prostatectomy

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Purpose: In large scale prospective studies, prostate-specific antigen (PSA)-screening not only decreased prostate cancer mortality, but also reduced biochemical recurrence (BCR) in patients undergoing radical prostatectomy (RP). We investigated the independent effect of the presence of PSA checked more than 1 year before diagnostic biopsy on the prognosis of patients undergoing RP in a real world setting without PSA-screening.

Materials and Methods: We reviewed the database of patients undergoing RP at Ajou University Hospital from March 1999 to May 2018. Clinicopathological features assessed were age, presence of lower urinary tract symptoms at presentation, presence of PSA checked over 1 year before biopsy, presence of PSA checked within 4 to 1 years of biopsy, last pre-biopsy PSA (pPSA), biopsy grade group (bGG), cT, cN, percentage of positive biopsy cores (PPBC), pathological GG (pGG), pT, pN, surgical margin, and index tumor diameter. The primary endpoint was BCR-free survival (BCRFS).

Results: Of 598 patients enrolled, 211 experienced BCR at the mean follow-up of 64±37 months. The 5-year and 10-year BCRFS were 62.8% and 53.9%, respectively. In multivariate analyses including clinical variables only, pPSA, bGG, cT, PPBC, and PSA within 4 to 1 years of biopsy independently affected BCRFS. In multivariate analyses including pathological variables only, pPSA, pGG, pT, pN, PSA checked over 1 year before biopsy and PSA checked within 4 to 1 years of biopsy independently affected BCRFS.

Conclusions: Patients who has checked PSA at least once beyond 1 year before diagnosis of prostate cancer show better BCRFS regardless of other factors.

Keywords: Cancer screening; Prostate cancer; Prostate-specific antigen; Recurrence; Retropubic prostatectomy

INTRODUCTION

Radical prostatectomy (RP) is the preferred treatment for patients with localized prostate cancer (PCa) and provides an excellent cancer control. However, biochemical recurrence (BCR) occurs in up to 40% after RP, requiring a salvage therapy, which often means added physical and financial burden [1]. Therefore, pre-, and postoperative patient education and counseling about the possibility of an additional therapy to achieve a long-term cancer control is

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crucial. Clinical stage, Gleason score and prostate-specific antigen (PSA) form the basis for the risk stratification to select appropriate treatment options and to predict the risk of BCR. Percentage of positive biopsy cores (PPBC), percent area with cancer and PSA density provide further prognostic information, but these are difficult to standardize [2]. Postoperatively, adverse pathological features or biochemical persistence dictates adjuvant therapy, but it is difficult to select those whose disease will eventually progress and benefit from an adjuvant therapy. Therefore, PSA monitoring and the institution of a salvage therapy at BCR is often a preferred alternative.

The introduction of PSA-screening in late 1980s has resulted in a dramatic shift towards diagnosis at earlier stage and a sharp decrease in PCa mortality [3]. However, the coincidental advances in the surgical technics and early detection and treatment of recurrent and progressive disease provided by PSA during the same period have also contributed to this decrease [4,5]. Moreover, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial showed that annual PSA-screening was ineffective at lowering mortality compared to non-screening control [6,7]. Thus, the role of PSA-screening in PCa mortality reduction remains uncertain and controversial in the United States.

In contrast, the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that PSA-screening performed at 4 years interval significantly reduced PCa mortality by 20% [8,9]. A long-term follow-up study of RP patients from the Rotterdam section of ESRPC has shown significantly better BCR-free and metastasis-free survival (MFS) in the screening group compared to the control group with a hazard ratio of 0.43 and 0.43 for BCR and 0.18 and 0.24 for metastasis after adjusting for standard preoperative and postoperative predictors, respectively [10]. While these measurable estimates can be used during perioperative shared clinical decision-making as a favorable claim for PSA-screening, they are not applicable in a real world setting where PSA-screening is not active. The purpose of this study was to analyze the effects of serial PSA check-up on the prognosis of patients undergoing RP in an environment where PSA-screening is not active and to provide a basis for regular screening needs.

MATERIALS AND METHODS

1. Patients and data collection

This study was approved by the Ajou University Hospital Institutional Review Board (AJIRB, approval number: MED-MDB-19-539). Because of the retrospective design of our study, the IRB waived the need to obtain informed consent from our patients. All consecutive patients who underwent RP from March 1999 to May 2018 at Ajou University Medical Center (AUMC) were eligible for this retrospective study. Most patients were diagnosed by transrectal prostate biopsy performed at AUMC. Our indications for transrectal biopsy were at least two consecutive PSA ≥4 ng/mL, or a palpable suspicious nodule on digital rectal examination. Preoperative magnetic resonance imaging of prostate was routinely taken to assess clinical stage. Bone scan was taken when bony metastasis was suspected. Patients with clinically localized or locally advanced disease received either open or robotic assisted (since 2008) radical retropubic prostatectomy. If clinically indicated, pelvic lymph node dissection was added. Adjuvant radiation therapy was not implemented in case of adverse pathological features. However, androgen deprivation therapy was usually initiated in the presence of pathological lymph node metastasis, which was considered equivalent to BCR in statistical analysis. Postoperatively, PSA was checked every 3 months during the first year, every 6 months during the second and the third year and yearly thereafter until clinically indicated. BCR was defined as a detectable PSA level ≥0.2 ng/mL and rising. All relevant PSA values were collected that included PSA checked at AUMC and Ajou University Health Promotion Center as well as outside PSA values derived from referral notes and attached lab reports, archival or current at the time of diagnosis. Clinical factors assessed were age at diagnosis of PCa, the last pre-biopsy PSA (pPSA), biopsy grade group (bGG), the PPBC, clinical T (cT) stage and clinical N (cN) stage. Pathological factors assessed were pathological grade group (pGG), pathological T (pT) stage, pathological N (pN) stage, surgical margin status and index tumor diameter. The 2014 ISUP criteria was used for grading of PCa [11].

2. Subgroups

We assumed that in an environment where a PSA-screening program is not active, cancer diagnosis induced by the presence of lower urinary tract symptoms (LUTS), i.e., opportunistic, would generally happen earlier than cancer diagnosed due to a serendipitously elevated PSA. So, those with and without LUTS at presentation were defined as group 1 and group 2, respectively.

We also assumed that the presence of at least one archival PSA checked >1 year before the diagnostic biopsy would be a favorable prognostic factor as it would probably mean one of the followings: a value within normal limits, an elevated value that prompted follow-up PSA that returned to within normal limits, or consecutively elevated values that

Table 1. Clinicopathological characteristics of 598 patients who underwent radical prostatectomy and grouped according to presence or absence of symptom at presentation and PSA at various time points before diagnosis

Variable	Total	Group 1 (n=323)	Group 2 (n=273)	p-value[a]	Group 3 (n=124)	Group 4 (n=474)	p-value[a]	Group 5 (n=103)	Group 6 (n=495)	p-value[a]
Age (y)	66.1±6.7	67.1±6.3	65.0±7.0	<0.001[b]	66.3±7.1	66.1±6.6	0.800[b]	66.4±7.4	66.1±6.6	0.684[b]
PSA (ng/mL)	10.5±10.2	10.3±9.3	10.6±11.1	0.787[b]	8.5±5.9	11.0±11.0	0.018[b]	8.1±5.9	11.0±10.8	0.008[b]
bGG	597	322	273		124	473		103	494	
1	93 (15.6)	50 (15.5)	43 (15.8)	0.599	28 (22.6)	65 (13.7)	0.008	25 (24.3)	68 (13.8)	0.004
2	184 (30.8)	97 (30.1)	86 (31.5)		44 (35.5)	140 (29.6)		37 (35.9)	147 (29.8)	
3	173 (29.0)	94 (29.2)	79 (28.9)		24 (19.4)	149 (31.5)		18 (17.5)	155 (31.4)	
4	44 (7.4)	20 (6.2)	24 (8.8)		12 (9.7)	32 (6.8)		10 (9.7)	34 (6.9)	
5	103 (17.3)	61 (18.9)	41 (15.0)		16 (12.9)	87 (18.4)		13 (12.6)	90 (18.2)	
cT	594	322	270		124	470		103	491	
≤2	431 (72.6)	235 (73.0)	195 (72.2)	0.186	91 (73.4)	340 (72.3)	0.828	78 (75.7)	353 (71.9)	0.709
3a	134 (22.6)	67 (20.8)	66 (24.4)		26 (21.0)	108 (23.0)		21 (20.4)	113 (23.0)	
≥3b	29 (4.9)	20 (6.2)	9 (3.3)		7 (5.6)	22 (4.7)		4 (3.9)	25 (5.1)	
cN	595	323	270		124	471		103	492	
0	573 (96.3)	312 (96.6)	259 (95.9)	0.668	123 (99.2)	450 (95.5)	0.055	103 (100.0)	470 (95.5)	0.029
1	22 (3.7)	11 (3.4)	11 (4.1)		1 (0.8)	21 (4.5)		0 (0.0)	22 (4.5)	
% positive biopsy cores	596	323	273		124	474		103	495	
≤25%	283 (47.5)	168 (52.0)	115 (42.1)	0.016	57 (46.0)	226 (47.7)	0.734	49 (47.6)	234 (47.3)	0.956
>25%	313 (52.5)	155 (48.0)	158 (57.9)		67 (54.0)	248 (52.3)		54 (52.4)	261 (52.7)	
pGG	594	320	272		124	470		103	491	
1	47 (7.9)	23 (7.2)	24 (8.8)	0.389	14 (11.3)	33 (7.0)	0.084	12 (11.7)	35 (7.1)	0.100
2	243 (40.9)	121 (37.8)	121 (44.5)		59 (47.6)	184 (39.1)		50 (48.5)	193 (39.3)	
3	201 (33.8)	117 (36.6)	84 (30.9)		33 (26.6)	168 (35.7)		29 (28.2)	172 (35.0)	
4	19 (3.2)	10 (3.1)	8 (2.9)		5 (4.0)	14 (3.0)		3 (2.9)	16 (3.3)	
5	84 (14.1)	49 (15.3)	35 (12.9)		13 (10.5)	71 (15.1)		9 (8.7)	75 (15.3)	
pT	598	323	273		124	474		103	495	
≤2	318 (53.2)	175 (54.2)	142 (52.0)	0.824	68 (54.8)	250 (52.7)	0.557	61 (59.2)	257 (51.9)	0.363
3a	205 (34.3)	107 (33.1)	97 (35.5)		38 (30.6)	167 (35.2)		32 (31.1)	173 (34.9)	
≥3b	75 (12.5)	41 (12.7)	34 (12.5)		18 (14.5)	57 (12.0)		10 (9.7)	65 (13.1)	
pN	598	323	273		124	474		103	495	
0	570 (95.3)	307 (95.0)	261 (95.6)	0.748	121 (97.6)	449 (94.7)	0.180	100 (97.1)	470 (94.9)	0.350
1	28 (4.7)	16 (5.0)	12 (4.4)		3 (2.4)	25 (5.3)		3 (2.9)	25 (5.1)	

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led to at least a previous negative biopsy. The possibility of consecutively elevated values with unrecommended or denied biopsy was excluded because this situation was mostly undocumented. Those with and without an archival PSA checked >1 year before the diagnostic biopsy were defined as group 3 and group 4, respectively.

A screening interval of 4 years in the ERSPC as opposed to an annual screening in the PLCO, is one of the differences in the trial setting cited to explain why PSA-screening in the ERSPC only had a significant effect in reducing PCa mortality. We assumed that the same cutoff of 4 years interval could also translate into some difference in prognosis. So, those with and without an archival PSA checked within 4 to 1 year of diagnostic biopsy were defined as group 5 and group 6, respectively.

3. Statistical analysis

The primary endpoint was BCR-free survival (BCRFS) and secondary endpoints included MFS and cancer-specific survival (CSS). Kaplan–Meier curve was used to estimate BCRFS, MFS, and CSS, and the log rank test was used to compare survival between groups. Cox proportional hazards model was used to calculate the hazard ratio of mode of presentation (symptomatic vs. incidental), the presence of PSA >1 year before biopsy, the presence of PSA within 4 to 1 year of biopsy, last pPSA, bGG, PPBC, T stage (cT and pT), N stage (cN and pN), pGG, surgical margin, and index tumor diameter on BCRFS. For multivariate analysis, four models were constructed. The first two models included only clinical variables and the last two models included only pathological variables, assuming their potential distinct applicability during pretreatment and post-treatment counseling, respectively. These models also included PSA-related factors that mutually excluded the presence of PSA >1 year before biopsy and the presence of PSA within 4 to 1 year of biopsy in each adjacent model. The same analysis was omitted for MFS and CSS due to small number of events and insignificance in survival difference between respective groups in the Kaplan–Meier analysis. SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

RESULTS

Total 631 patients had received RP among which 29 and 4 were excluded due to less than 12 months follow-up and no remaining cancer in the final pathology, respectively. The remaining 598 patients were enrolled in this study. Seventeen, 52, and 529 patients had received 6-core, 10-core, and 12-core biopsy, respectively. The clinicopathological charac-

Table 1. Continued

Variable	Total	Group 1 (n=323)	Group 2 (n=273)	p-value[a]	Group 3 (n=124)	Group 4 (n=474)	p-value[a]	Group 5 (n=103)	Group 6 (n=495)	p-value[a]
SM	595	321	272		123	472		102	493	
Negative	253 (42.5)	148 (46.1)	104 (38.2)	0.141	53 (43.1)	200 (42.4)	0.856	46 (45.1)	207 (42.0)	0.643
Positive	342 (57.5)	173 (53.9)	168 (61.8)		70 (56.9)	272 (57.6)		56 (54.9)	286 (58.0)	
Index tumor diameter (mm)[c]	17.7±9.1	17.8±9.1	17.7±9.1	0.924[b]	16.1±8.2	18.1±9.3	0.037[b]	15.1±7.1	18.3±9.4	0.002[b]

Values are presented as mean±standard deviation, number only, or number (%).
PSA, prostate-specific antigen; bGG, biopsy grade group; cT, clinical T stage; cN, clinical N stage; pGG, pathological GG; pT, pathological T stage; pN, pathological N stage; SM, surgical margin; Group 1, symptomatic; Group 2, incidental; Group 3, presence of PSA >1 year before biopsy; Group 4, absence of PSA >1 year before biopsy; Group 5, presence of PSA within 4 to 1 year of biopsy; Group 6, absence of PSA within 4 to 1 year of biopsy.
[a]:Chi-square test. [b]:Student's t-test. [c]:Index tumor diameter value was available in 516 patients.

teristics of the patients and the results of subgroup analysis are presented in the Table 1. As can be anticipated, the age at presentation was significantly higher in the group 1 compared to the group 2. Also, the PPBC, dichotomized into ≤25% (or ≤3 cores in 12-core biopsy) and >25%, was significantly lower in the group 1. PSA at presentation was significantly lower in the group 3 and 5 compared to the group 4 and 6, respectively. In addition, cN stage was significantly lower in the group 5 compared to the group 6. Among pathological variables, only the index tumor diameter was significantly different between group 3 and 4, and between group 5 and 6.

During the median follow-up of 65.0 months (range, 12–196 mo), 211 patients experienced BCR, 13 patients developed metastasis and 3 patients died of PC. The 5-year and 10-year BCRFS were 62.8% and 53.9%, respectively. The Kaplan–Meier analysis showed a significantly better BCRFS in the group 3 compared to the group 4 and in the group 5 compared to the group 6. However, there was no significant difference in BCRFS between the group 1 and 2 (Fig. 1). As for MFS and CSS, there was no significant difference between respective groups.

The univariate cox regression analysis revealed the presence of PSA >1 year before biopsy and the presence of PSA within 4 to 1 year of biopsy to be significant prognostic factors for BCRFS along with pPSA, bGG, cT, cN, pGG, PPBC, pT, pN, surgical margin status and index tumor diameter (Table 2). However, symptom at presentation did not predict BCR.

The multivariate analysis with clinical variables (model 1 and 2) revealed the presence of PSA checked within 4 to 1 year of biopsy (hazard ratio, 0.597; p=0.031) to be a significant prognostic factor for BCRFS independent of other significant prognostic factors such as pPSA, bGG, cT, and PPBC (Table 3). Multivariate analysis with pathological variables (model 3 and 4) revealed the presence of PSA >1 year before biopsy (hazard ratio, 0.611; p=0.030) and the presence of PSA checked within 4 to 1 year of biopsy (hazard ratio, 0.580; p=0.042) to be significant prognostic factors for BCRFS independent of other significant prognostic factors such as pPSA, pGG, pT, and pN (Table 4).

DISCUSSION

The importance of PSA in the early diagnosis of PCa is

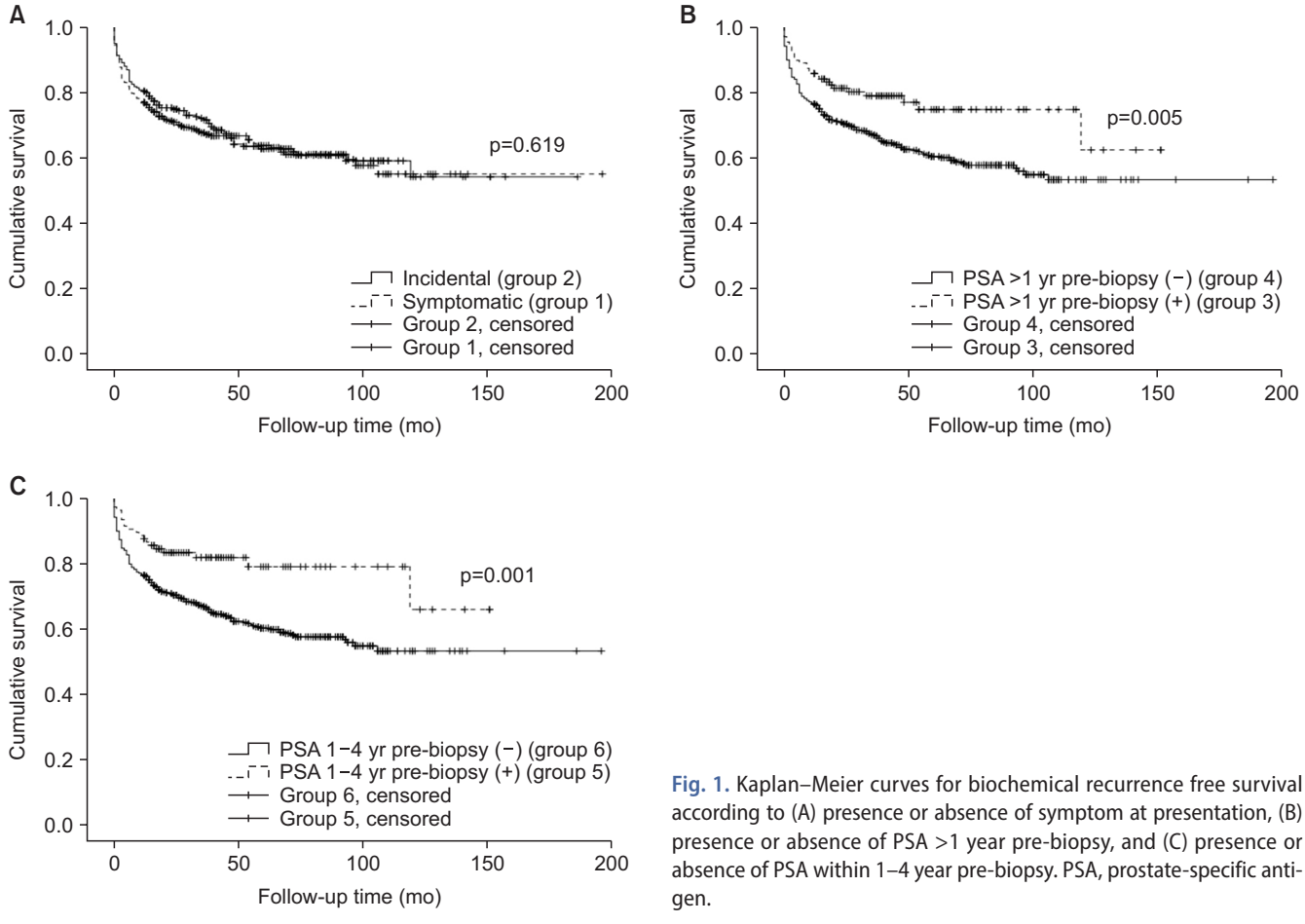

Fig. 1. Kaplan–Meier curves for biochemical recurrence free survival according to (A) presence or absence of symptom at presentation, (B) presence or absence of PSA >1 year pre-biopsy, and (C) presence or absence of PSA within 1–4 year pre-biopsy. PSA, prostate-specific antigen.

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Table 2. Univariate Cox regression analysis of potential prognostic factors for biochemical recurrence after radical prostatectomy

Variable	Hazard ratio (95% confidence interval)	p-value
Age	1.001 (0.980–1.021)	0.616
Symptomatic (vs. incidental)	0.933 (0.710–1.225)	0.616
Presence of PSA >1 year before biopsy	0.572 (0.384–0.852)	0.006
Presence of PSA within 4 to 1 year of biopsy	0.485 (0.306–0.769)	0.002
Last PSA before biopsy	1.034 (1.027–1.041)	<0.001
bGG (vs. group 5)		<0.001
Group 1	0.219 (0.130–0.370)	<0.001
Group 2	0.209 (0.139–0.313)	<0.001
Group 3	0.466 (0.333–0.653)	<0.001
Group 4	0.500 (0.297–0.842)	0.009
cT (vs. 3b)		<0.001
≤2	0.261 (0.161–0.425)	<0.001
3a	0.702 (0.424–1.160)	0.167
cN0 (vs. 1)	0.347 (0.205–0.588)	<0.001
% positive biopsy cores ≤25% (vs. >25%)	0.322 (0.236–0.438)	<0.001
pGG (vs. group 5)		<0.001
Group 1	0.104 (0.045–0.240)	<0.001
Group 2	0.141 (0.096–0.206)	<0.001
Group 3	0.302 (0.217–0.421)	<0.001
Group 4	0.301 (0.231–0.932)	0.031
pT (vs. 3b)		<0.001
≤2	0.095 (0.066–0.137)	<0.001
3a	0.253 (0.183–0.351)	<0.001
pN0 (vs. 1)	0.133 (0.088–0.201)	<0.001
SM negative	0.348 (0.252–0.479)	<0.001
Mean index tumor diameter	2.098 (1.790–2.459)	<0.001

PSA, prostate-specific antigen; bGG, biopsy grade group; cT, clinical T stage; cN, clinical N stage; pGG, pathological GG; pT, pathological T stage; pN, pathological N stage; SM, surgical margin.

Table 3. Multivariate Cox regression analysis of potential clinical factors for biochemical recurrence after radical prostatectomy

Variable	Model 1		Model 2	
	Adjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
Presence of PSA >1 year before biopsy	0.684 (0.456–1.026)	0.067	-	-
Presence of PSA within 4 to 1 year of biopsy	-	-	0.597 (0.374–0.953)	0.031
Last PSA before biopsy	1.025 (1.016–1.034)	<0.001	1.025 (1.016–1.033)	<0.001
bGG (vs. group 5)		<0.001		<0.001
Group 1	0.476 (0.271–0.835)	0.010	0.478 (0.273–0.838)	0.010
Group 2	0.328 (0.213–0.506)	<0.001	0.326 (0.211–0.503)	<0.001
Group 3	0.647 (0.453–0.925)	0.017	0.640 (0.448–0.915)	0.014
Group 4	0.638 (0.375–1.084)	0.097	0.534 (0.373–1.077)	0.092
cT (vs. 3b)		0.013		0.015
≤2	0.568 (0.327–0.987)	0.045	0.582 (0.336–1.009)	0.054
3a	0.886 (0.522–1.504)	0.886	0.904 (0.533–1.533)	0.709
cN0 (vs. 1)	0.720 (0.406–1.278)	0.262	0.721 (0.407–1.278)	0.262
% positive biopsy cores ≤25% (vs. >25%)	0.484 (0.347–0.676)	<0.001	0.485 (0.346–0.677)	<0.001

PSA, prostate-specific antigen; bGG, biopsy grade group; cT, clinical T stage; cN, clinical N stage; -, not applicable.

Table 4. Multivariate Cox regression analysis of pathological prognostic factors and PSA-related prognostic factors for biochemical recurrence after radical prostatectomy

Variable	Model 3		Model 4	
	Adjusted hazard ratio (95% confidence interval)	p-value	Adjusted hazard ratio (95% confidence interval)	p-value
Presence of PSA >1 year before biopsy	0.611 (0.391–0.955)	0.030	-	-
Presence of PSA within 4 to 1 year of biopsy	-	-	0.580 (0.343–0.981)	0.042
Last PSA before biopsy	1.024 (1.005–1.043)	0.012	1.025 (1.006–1.044)	0.011
pGG (vs. group 5)		0.004		0.020
Group 1	0.432 (0.158–1.183)	0.102	0.425 (0.155–1.165)	0.096
Group 2	0.397 (0.249–0.633)	<0.001	0.388 (0.244–0.617)	<0.001
Group 3	0.549 (0.362–0.833)	0.005	0.553 (0.364–0.839)	0.005
Group 4	0.629 (0.304–1.301)	0.211	0.604 (0.293–1.245)	0.172
pT (vs. 3b)		<0.001		<0.001
≤2	0.208 (0.116–0.373)	<0.001	0.224 (0.127–0.396)	<0.001
3a	0.353 (0.238–0.522)	<0.001	0.366 (0.249–0.539)	<0.001
pN0 (vs. 1)	0.411 (0.243–0.696)	0.001	0.397 (0.235–0.671)	0.001
SM negative	0.807 (0.498–1.310)	0.386	0.778 (0.481–1.258)	0.305
Mean index tumor diameter	1.192 (0.956–1.487)	0.119	1.186 (0.952–1.478)	0.129

PSA, prostate-specific antigen; pGG, pathological GG; pT, pathological T stage; pN, pathological N stage; SM, surgical margin; -, not applicable.

well known by the general population. PSA screening had a significant effect on epidemiology, reducing the rate of metastases at diagnosis by 80% and the age adjusted PCa mortality rate by more than 53% [3,12]. Interim analyses of PLCO and ERSPC trials had also shown that increasing rounds of PSA screening resulted in lower stage, grade, and tumor volume in cancers detected in subsequent rounds compared to those diagnosed in the first round screening [13,14]. In this respect, the lack of survival advantage of PSA screening in the PLCO trial has been subject to much controversy [6,15]. A recent reevaluation of PSA testing rates in the PLCO trial suggested that more than 80% of the participants in the control arm have undergone at least 1 PSA test during the trial, which was much higher than the expected PSA contamination rate [16]. This and other unforeseen flaws in the trial design have compromised the validity of the trial itself, and the urologists are left with the positive result of ERSPC trial alone to appraise the value of PSA in PCa screening.

Risk stratification of clinically localized PCa is primarily based on cT stage, biopsy grade, and PSA [2]. Additional information such as the PPBC, the percent area with cancer and PSA density serves to subclassify low risk and intermediate risk into extremely low and favorable risk, respectively. However, the main purpose of these subclassifications is to better define candidates for active surveillance. So, in terms of prediction of post-RP survival, cT stage, biopsy grade, and PSA remain as the only validated predictors. Our study showed for the first time that the presence of a PSA checked >1 year before the diagnostic biopsy outside of a PSA-screening program, independently improves PCa prognosis in terms of BCR in patients undergoing RP. It also demonstrated that a PSA checked within 4 to 1 year of biopsy will be of best value. However, we failed to show that archival PSA improves MFR and CSS. Nevertheless, our results may benefit RP patients by providing an additional information to risk stratification in estimating the probability of BCR during preoperative and postoperative counseling.

The precise mechanism by which the presence of PSA checked >1 year and within 4 to 1 year of biopsy improves BCRFS independent of other factors is difficult to explain. We hypothesized that the lead time provided by an earlier PSA would result in smaller tumor volume at diagnosis, which could be best expressed by lower PPBC and lower tumor volume in the prostatectomy specimen. We used PPBC and the diameter of the index tumor reported by the pathologist as proxy of tumor volume and found the index tumor volume only to be associated with the presence of PSA checked >1 year and within 4 to 1 year of biopsy. It is well recognized that most PCas are multifocal with different foci often showing different Gleason scores, and probably being of different clonal origins [17]. Therefore, high PPBC in our cohort would more closely reflect multifocality rather than a large tumor volume. Our results corroborate but also differs from the study by Loeb et al. [10] in which RP patients from the Rotterdam section of ESRPC have shown significantly better BCR-free and MFS in the screening group compared to the control group. In their study however, the incorpora-

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tion of tumor volume in the multivariate analysis removed the benefit of screening, implying that improved outcome in the screening group was mediated by a significantly lower tumor volume [10]. In our cohort of patients, the result was opposite, with the presence of PSA checked >1 year or within 4 to 1 year of biopsy being prognostic for BCRFS, independent of proxy of tumor volume. Intricate PSA kinetics may play a role, which cannot be demonstrated in complex clinical settings.

Our assumption that patients with LUTS will be diagnosed earlier than asymptomatic patients with serendipitously elevated PSA was not proven in our study. The most probable explanation is that PCa usually arises in the peripheral zone and does not affect urinary tract obstruction and therefore does not cause symptoms [18]. Therefore, it is not correct to simply assume that people with lower urinary tract symptoms will get PSA tests earlier and have cancer detected earlier. In an environment where PSA screening is not active, efforts to get PSA tested early regardless of symptoms will be required.

There are some limitations in this study. Because of the retrospective nature of our study, patients number allocated to subgroups were not balanced. The study by Loeb et al. [10] also showed unbalanced patients' number which did not poorly affect the results, and we believe our results reflect the real-life situation. Also, we cannot guarantee that all PSA values were collected. In addition, because PSA testing was conducted at various facilities, PSA screening intervals were not constant, and the test quality was not well controlled. This could have seriously affected the results. While these limitations exist and require careful interpretation, overall trends indicate that PSA screening is essential.

CONCLUSIONS

Our results suggest that patients who has checked PSA at least once beyond 1 year before diagnosis of PCa show better BCRFS regardless of other clinical and pathological factors. PSA check-up every 4 years seems adequate, but optimal time interval between PSA needs further investigation in order to incorporate PSA-screening in the National Cancer Screening Program in the future.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Sun Il Kim. Data acquisition: Sung Gon Park. Statistical analysis: Sung Gon Park. Data analysis and interpretation: Sung Gon Park and Sun Il Kim. Drafting of the manuscript: Sung Gon Park. Critical revision of the manuscript: Kang Hee Shim, Seol Ho Choo, and Se Joong Kim. Obtaining funding: Sun Il Kim. Administrative, technical, or material support: Kang Hee Shim. Supervision: Sun Il Kim. Approval of the final manuscript: Sun Il Kim.

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