Asian Journal of Andrology (2021) 23, 36–40
www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Prostate Cancer

A novel screening strategy for clinically significant prostate cancer in elderly men over 75 years of age

Hiroaki Iwamoto, Kouji Izumi, Suguru Kadomoto, Tomoyuki Makino, Renato Naito, Hiroshi Yaegashi, Kazuyoshi Shigehara, Yoshifumi Kadono, Atsushi Mizokami

A standard modality for prostate cancer detection in men 75 years and older has not been established. A simple screening method for elderly patients is needed to avoid unnecessary biopsies and to effectively diagnose prostate cancer. A retrospective study was conducted on elderly patients who had prostate biopsy at Kanazawa University Hospital (Kanazawa, Japan) between 2000 and 2017. Of the 2251 patients who underwent prostate biopsy, 254 had clinically significant prostate cancer (CSPC) with a Gleason score (GS) of ≥7 and 273 had a GS of <7 or no malignancy. In this study, patients aged 75 years or older were classified as elderly patients. GS ≥7 was characterized by a prostate-specific antigen (PSA) of the maximum area under the curve of 12 ng ml^{-1} with a sensitivity of 76.2% and a specificity of 73.2%. For PSA levels between 4 ng ml^{-1} and 12 ng ml^{-1}, based on the maximum area under the curve, patients with three or four of the following factors may present a GS of ≥7: percent free PSA >24, PSA density ≥0.24 ng ml^{-2}, positive findings on digital rectal examination, and transrectal with 90.0% sensitivity and 67.4% specificity. In this study, we found that raising the PSA cutoff to 12 ng ml^{-1} for CSPC in elderly individuals can significantly reduce unnecessary prostate biopsies. Furthermore, CSPC could be efficiently discovered by combining the four supplementary markers in patients with a PSA level of 4–12 ng ml^{-1}. By performing this screening for elderly men over 75 years of age, unnecessary biopsies may be reduced and CSPC may be detected efficiently.

Asian Journal of Andrology (2021) **23**, 36–40; doi: 10.4103/aja.aja_39_20; published online: 28 July 2020

Keywords: biopsy; elderly; Gleason score; percent free prostate-specific antigen; prostate cancer; prostate-specific antigen

INTRODUCTION

Prostate cancer is the most common cancer among men and the second leading cause of cancer-related mortality.[1] Radical treatments, such as prostatectomy and radiation therapy, are usually performed in patients with localized or locally advanced prostate cancer with an expected survival longer than 10 years.[2] Elderly men generally have a shorter life expectancy and pose higher risk for potential harm from prostate cancer screening.[3] In men above 70 years, prostate biopsies are associated with a higher risk of complications and longer hospital stay.[4] Moreover, previous report has shown that prostate cancer develops slowly, the 10-year survival rate is higher than 95%, and overdiagnosis is common in elderly men.[5] The American Urological Association Early Detection of Prostate Cancer guidelines (https://www.auanet.org/guidelines/prostate-cancer-early-detection-guideline) do not recommend routine prostate-specific antigen (PSA) screening in men aged 70 years and older or in those with less than a 10- to 15-year life expectancy. The prostate cancer guidelines of the European Association of Urology (https://uroweb.org/guideline/prostate-cancer/) indicate that PSA screening may not be effective in men with a life expectancy <15 years. Some elderly patients have life-threatening, clinically significant prostate cancer (CSPC) and need help through effective prostate cancer detection. A standard modality to detect prostate cancer in elderly patients has not been established. Hence, this study developed a simple screening method to avoid unnecessary biopsies and to effectively diagnose CSPC in elderly patients.

PATIENTS AND METHODS

Patients

The charts of patients who underwent prostate biopsy at Kanazawa University Hospital (Kanazawa, Japan) between January 2000 and December 2017 were reviewed, and relevant data were collected and retrospectively analyzed. Patients 75 years or older, whose average life expectancy in Japan is considered to be approximately 10 years, were classified as elderly patients. According to the Ministry of Health, Labor and Welfare's 2015 Life Table, the life expectancy of a 75-year-old Japanese was 12 years. This study was approved by the Medical Ethics Committee of Kanazawa University (No. 2019-083). Since this was a retrospective study without intervention, the content of the study was posted and consent was obtained.

Data collection

The collected medical information included serum PSA level, percent free PSA (%fPSA), PSA density (PSAD), digital rectal examination (DRE) results, transrectal ultrasonography (TRUS) results, prostate volume (PV), and prostate biopsy pathology. The PSAD was obtained by dividing the serum PSA levels by the PV, which was determined during TRUS. Overall survival (OS) was retrospectively analyzed.

Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa 920-8640, Japan.
Correspondence: Dr. K Izumi (azuizu2003@yahoo.co.jp)
Received: 02 November 2019; Accepted: 15 May 2020

Pathological diagnosis

The patients underwent TRUS-guided systematic biopsies of 10 cores that included lateral and mid-lobar cores at the base, middle, and apex of each prostate lobe. The biopsy specimens were analyzed by a genitourinary pathologist from the Kanazawa University Hospital. CSPC was defined as any cancer with a Gleason score (GS) of 3 + 4 or higher.[6]

Statistical analyses

Prism version 5 (GraphPad, San Diego, CA, USA) was used for all the statistical analyses. The Mann–Whitney U test and Chi-square test were used to compare continuous variables and categorical variables, respectively. The best-fit receiver operating characteristic (ROC) curve and the corresponding area under the ROC curve (AUC) estimates were calculated, followed by the 95% confidence interval (CI). Then, the cutoff values of PSA, %fPSA, and PSAD were obtained. In the analyses, $P < 0.05$ was considered statistically significant. OS was estimated using the Kaplan–Meier method.

RESULTS

Of the 2251 patients who had prostate biopsy, 529 elderly patients were analyzed retrospectively. Two prostate cancer patients were excluded because their GS were not available, but among those included, 254 CSPC patients had a GS ≥7 and 273 patients had a GS <7 or no malignancy. Of 273 non-CSPC patients, 66 were diagnosed with prostate cancer with GS <7. Of 254 CSPC patients, 165 patients received androgen deprivation therapy, 54 patients received radiation therapy, 6 patients underwent radical prostatectomy, and 29 patients were unknown.

Table 1 shows the patient characteristics. The median age, PSA level, and PSAD of patients with a GS <7 or no malignancy were 78 years, 8.3 ng ml^{-1}, and 0.21 ng ml^{-2}, respectively, and were significantly lower than those of CSPC patients (all $P < 0.0001$). Their median %fPSA was 22.2 and was significantly higher than that of CSPC patients ($P < 0.0001$). The rates of abnormal findings in DRE and TRUS in patients with a GS <7 or no malignancy were 21.3% (30/141) and 23.3% (35/150), respectively, which were significantly lower than those of CSPC patients (both $P < 0.0001$).

Figure 1 shows the relationship between age and GS, T stage, N stage, or M stage. The percentages of patients with CSPC, T3–T4, and N1 or M1 were 79.1%, 38.8%, and 25.3%, respectively. The percentage of patients with CSPC, T3–T4, and N1 or M1 increased significantly as age increased ($P = 0.0012$, 0.0014, and <0.0001 for CSPC, T3-T4, and N1 or M1, respectively).

The diagnostic performance of the PSA level for CSPC is illustrated in the ROC curve shown in **Figure 2a** and **2b**. The AUC value of the PSA level was 0.799, and the PSA level of the maximum AUC value was 12 ng ml^{-1}. The sensitivity and specificity of PSA >12 ng ml^{-1} were 76.6% and 73.2%, respectively.

The diagnostic performances of %fPSA and PSAD for CSPC are illustrated in the ROC curves shown in **Figure 2c**–**2f**. The AUC values of %fPSA and PSAD were 0.696 and 0.735, respectively, while the %fPSA and PSAD of the maximum AUC value were 24 and 0.24 ng ml^{-2}, respectively. The sensitivity and specificity of %fPSA <24 were 70.3% and 60.9%, respectively, and the sensitivity and specificity of PSAD ≥0.24 ng ml^{-2} were 69.9% and 69.8%, respectively.

Table 2 presents the diagnostic performance of DRE and TRUS for CSPC. The sensitivity and specificity of positive CSPC by DRE were 39.4% and 86.4%, respectively, while the sensitivity and specificity of positive CSPC by TRUS were 53.8% and 81.7%, respectively.

When %fPSA was <24, PSAD was ≥0.24 ng ml^{-2}, the DRE was positive, and TRUS was positive, 1 point was assigned for each of the four factors in 53 patients with complete data; 96.8% of patients (30/31) had a total score <2 and a GS <7 or no malignancy, whereas 39.1% (9/23) had a total score ≥2 and were diagnosed with CSPC

Table 1: Patient characteristics

Variable	*Gleason score ≥7*	*Gleason score <7 or no malignancy*	*P*
Age (year), median (range)	79 (75–95)	78 (75–86)	0.001
Patient (*n*)	254	273	0.0006
75–79 years	142	189	
80–84 years	83	73	
≥85 years	29	11	
PSA (ng ml^{-1}), median (range)	29.2 (2.2–10998.0)	8.3 (0.06–195.0)	<0.0001
75–79 years	19.9 (2.5–6657)	8.4 (0.06–104.4)	<0.0001
80–84 years	29.4 (2.2–10998.0)	7.7 (0.6–195.0)	<0.0001
≥85 years	106.0 (2.6–3492.4)	8.4 (4.4–96.0)	<0.0001
%fPSA, median (range)	14 (4.3–47)	22.2 (1.5–74.3)	<0.0001
75–79 years	13.5 (4.3–30.2)	21.2 (1.5–74.3)	<0.0001
80–84 years	14 (6–47)	24.5 (9–42)	<0.0001
≥85 years	12 (6–21)	30.2 (5–47)	<0.0001
PSAD (ng ml^{-2}), median (range)	0.82 (0.09–306.77)	0.21 (0.003–2.06)	<0.0001
75–79 years	0.70 (0.09–306.77)	0.21 (0.003–2.06)	<0.0001
80–84 years	0.86 (0.11–179.18)	0.21 (0.07–1.58)	0.0013
≥85 yeas	2.61 (0.10–65.77)	0.18 (0.09–0.59)	<0.0001
DRE (*n*)			
Positive	110	30	<0.0001
Negative	59	111	
TRUS (*n*)			
Positive	128	35	<0.0001
Negative	48	115	

PSA: prostate-specific antigen; %fPSA: percent free PSA; PSAD: PSA density; DRE: digital rectal examination; TRUS: transrectal ultrasonography

(**Table 3**). The sensitivity and specificity of scores >2 were 90.0% and 67.4%, respectively.

Basing on the results, a CSPC screening algorithm for elderly men over 75 years was developed, as shown in **Figure 3**. First, the PSA test should be done in elderly patients over the age of 75. Patients with a PSA <4 ng ml^{-1} should receive a regular follow-up, while those with a PSA of 12 ng ml^{-1} or higher should undergo prostate biopsy. Patients with a PSA level of 4–12 ng ml^{-1} are evaluated with the following supplementary markers. %fPSA <24, PSAD ≥0.24 ng ml^{-2}, positive DRE, and positive TRUS are assigned with 1 point each, and patients received 0–4 points. Prostate biopsy is recommended for those with 2 or more points and follow-up observation for those with scores lower than 2 points. **Supplementary Figure 1** shows overall survival. There was no significant difference regardless of the level of PSA, the level of score, or the presence or absence of cancer (P = 0.66, 0.8, and 0.46, respectively).

Table 2: Relationship between digital rectal examination/transrectal ultrasonography findings and clinically significant prostate cancer in patients with prostate-specific antigen levels from 4 ng ml^{-1} to 12 ng ml^{-1}

Variables	*Gleason score ≥7*	*Gleason score <7 or no malignancy*	*Total*
DRE, *n* (%)			
Positive	13 (48.1)	14 (51.9)	27
Negative	20 (18.3)	89 (81.7)	109
Total	33 (24.3)	103 (75.7)	136
TRUS, *n* (%)			
Positive	21 (51.2)	20 (48.8)	41
Negative	18 (16.8)	89 (83.2)	107
Total	39 (26.4)	109 (73.6)	148

DRE: digital rectal examination; TRUS: transrectal ultrasonography

Table 3: Relationship between the total score of supplementary markers and clinically significant prostate cancer

Variables	*Point*	*Score*	*0*	*1*	*2*	*3*	*4*
%fPSA<24	1	GS ≥7	0	1	5	0	4
PSAD≥0.24	1	(%)	(0)	(2.3)	(11.6)	(0)	(9.3)
DRE positive	1	GS <7 or no malignancy	19	10	13	1	0
TRUS positive	1	(%)	(44.0)	(23.3)	(30.2)	(2.3)	(0)

PSA: prostate-specific antigen; %fPSA: percent free PSA; PSAD: PSA density; DRE: digital rectal examination; TRUS: transrectal ultrasonography

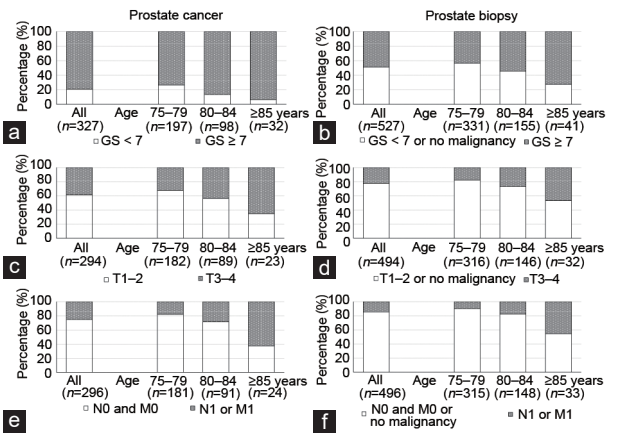

Figure 1: The distribution of clinical factors across the range of prostate cancer patient ages. (**a**) The distribution of GS indicates the percentage the percentage of GS ≥7 significantly increased as age increased (P = 0.0012). (**b**) The distribution of T stage indicates the percentage of T3–T4 significantly increased as age increased (P = 0.0014). (**c**) The distribution of the presence of metastasis (N or M) indicates the percentage of meta (+) significantly increased as age increased (P < 0.0001). (**d**) The distribution of GS indicates the percentage the percentage of GS ≥7 significantly increased as age increased (P = 0.0002). (**e**) The distribution of T stage indicates the percentage of T3–T4 significantly increased as age increased (P = 0.0001). (**f**) The distribution of the presence of metastasis (N or M) indicates the percentage of metastasis significantly increased as age increased (P < 0.0001). Patients for which no data were available were omitted. GS: Gleason score.

DISCUSSION

The American Urological Association and the European Association of Urology do not recommend routine PSA screening in elderly men with less than a 10- to 15-year life expectancy. The rate at which patients in Japan are subjected to PSA testing is still inadequate,

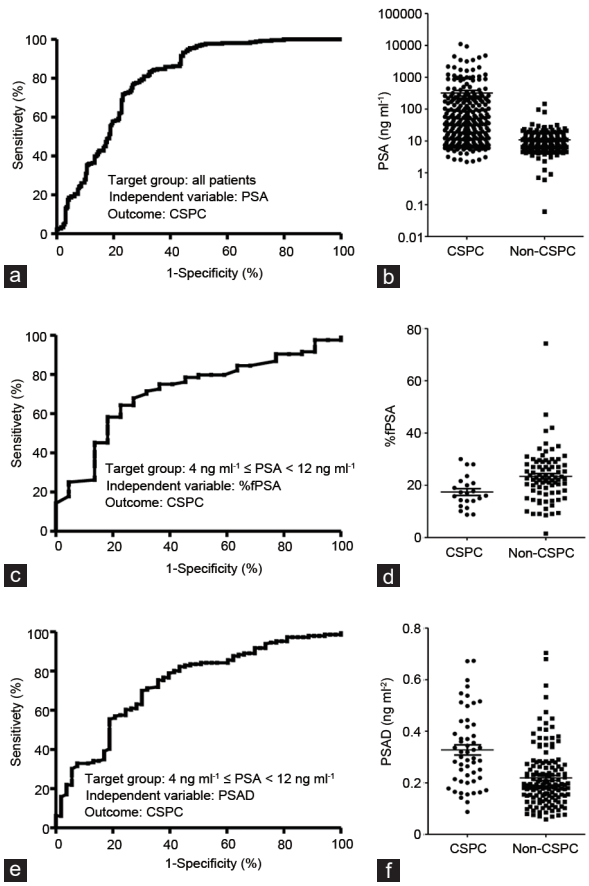

Figure 2: (**a**) ROC curve of PSA for CSPC and the PSA plot. AUC values of PSA level was 0.799, and PSA level of the maximum AUC value was 12 ng ml^{-1}. The sensitivity and specificity of PSA >12 ng ml^{-1} were 76.6% and 73.2%, respectively. (**b**) Median PSA of CSPC is significantly higher than non-CSPC (P = 0.0001). (**c**) ROC curves and plots of %fPSA for CSPC in patients with PSA levels from 4 ng ml^{-1} to 12 ng ml^{-1}. AUC values of %fPSA was 0.696, and %fPSA of the maximum AUC value was 24. The sensitivity and specificity of %fPSA <24 were 70.3% and 60.9%, respectively. (**d**) Median %fPSA of CSPC is significantly higher than non-CSPC (P = 0.0001). (**e**) ROC curves and plots of PSAD for CSPC in patients with PSA levels from 4 ng ml^{-1} to 12 ng ml^{-1}. AUC value of PSAD was 0.735, and PSAD of the maximum AUC value was 0.24. The sensitivity and specificity of PSAD >0.24 ng ml^{-2} were 69.9% and 69.8%, respectively. (**f**) Median PSAD of CSPC is significantly higher than non-CSPC (P = 0.0001). PSA: prostate-specific antigen; CSPC: clinically significant prostate cancer; non-CSPC: Gleason score <7 or no malignancy; %fPSA: percent free PSA; PSAD: PSA density; AUC: area under the ROC curve; ROC: receiver operating characteristic.

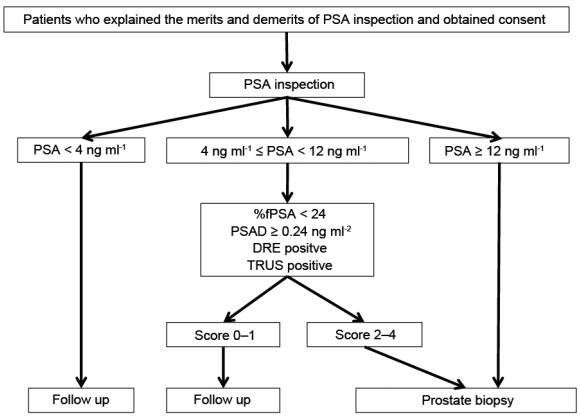

Figure 3: CSPC screening algorithm for elderly men over 75 years of age. The PSA test will be performed on elderly patients over the age of 75 years who have agreed with and explained the merits and demerits of the PSA test. Patients with PSA <4 ng ml^{-1} should be followed up. Patients with PSA 12 ng ml^{-1} or more should undergo urological examination followed by prostate biopsy. Patients with PSA 4–12 ng ml^{-1} are evaluated by the following supplementary markers. %fPSA <24, PSAD ≥0.24 ng ml^{-2}, DRE positive, and TRUS positive are regarded as 1 point each and scored as a total of 4 points, and if it is 2 points or more, prostate biopsy is performed. If it is less than 1 point, follow-up observation is needed. CSPC: clinically significant prostate cancer; PSA: prostate-specific antigen; %fPSA: percent free PSA; PSAD: PSA density; DRE: digital rectal examination; TRUS: transrectal ultrasonography.

and several undetected prostate cancers may still need treatment, especially those in the elderly. **Figure 1** presents the CSPC and advanced prostate cancer percentage in elderly patients and how they increase as age increases, indicating that several prostate cancers still require treatment, even in the elderly population. However, elderly men generally have a shorter life expectancy and pose a higher risk of potential harm from prostate cancer screening.[3] Moreover, biopsy in patients over 70 years has been associated with an almost fourfold increase in the risk of complications.[4] Thus, unnecessary biopsies should be reduced and effectively diagnose CSPC in elderly patients. However, urologists have not yet established a definite consensus on how to manage men aged 70 years and older with elevated PSA. PSA levels are known to rise with age,[7,8] but according to previous reports, the age-specific PSA reference range in Asians aged 70–79 years is 5.37–6.5 ng ml^{-1}.[7,8] **Figure 2** shows the possibility of raising the PSA cutoff to 12 ng ml^{-1} to detect CSPC in the elderly. The sensitivity and specificity of PSA >4 ng ml^{-1} were 97.2% and 4.8%, respectively, whereas the sensitivity and specificity of PSA >12 ng ml^{-1} were 76.6% and 73.2%, respectively. If the cutoff value is PSA >4 ng ml^{-1} in the elderly, the specificity will be very low, resulting in an increase in unnecessary prostate biopsies. Raising the PSA cutoff to 12 ng ml^{-1} may significantly reduce unnecessary prostate biopsies.

When the PSA cutoff value is set to 12 ng ml^{-1} in elderly individuals, the correspondence of these patients with PSA levels of 4–12 ng ml^{-1} should be considered an efficient detection of CSPC. %fPSA, PSAD, DRE findings, and TRUS findings have been found useful as supplementary markers for prostate cancer detection.[9–13] The relationship between the mentioned markers and CSPC was analyzed in patients with PSA levels from 4 ng ml^{-1} to 12 ng ml^{-1}. The sensitivity and specificity when the total score was ≥2 were 90.0% and 67.4%, respectively. Basing on the results, a CSPC screening algorithm for elderly individuals over 75 years of age was developed, as shown in **Figure 3**. The screening may reduce unnecessary biopsies and efficiently detects CSPC. In a report from China, PSAD, TRUS findings, and the prostate imaging reporting and data system (PI-RADS) score were factors that could be used to predict CSPC in elderly patients over 75 years, and PI-RADS version 2 score has been found to be very useful in predicting CSPC.[14–16] A PI-RADS version 2 score of 3–5 yielded a sensitivity of 97.4%, a specificity of 50.9%, and an AUC of 0.74 in predicting CSPC.[15] However, it is difficult to perform multiparametric magnetic resonance imaging (MRI) in elderly patients with high PSA, and it may also be challenging because this imaging modality can only be performed at general hospitals. The proposed screening method is very simple and can be implemented by any urologist. As shown in **Figure 1**, in this study, the proportion of CSPC patients increased with age. This result suggests that age may be a predictor of CSPC. However, as mentioned earlier, this is a retrospective study and it was the responsibility of the attending physician to decide whether to perform a biopsy. It seems that the criteria for performing a biopsy were getting stricter with age. This is inferred from the very high median PSA of 106 ng ml^{-1} in patients aged 85 years and older diagnosed with GS >7. In addition, only 40 patients aged 85 years or older who underwent prostate biopsy are small. Therefore, we did not include age as a factor in predicting CSPC.

This study has several limitations. Our study was retrospective study, and the decision to perform a prostate biopsy was at the discretion of the attending physician. Moreover, patients 75 years and older were categorized in a single group. This may be a limitation because the PSA cutoff value could be further increased in a group of men 85 years and older. The upper age limit for PSA testing has also not been considered. The sample size of this study was not large, and the number of cases with complete data to derive scoring was small. Additionally, the health assessments of elderly patients were left to the discretion of the attending physician. The G8 geriatric screening tool has been reported to help predict the prognosis cancer patients.[17] The International Society of Geriatric Oncology working group recommended that the G8 geriatric screening tool be used as a guideline for medical care and to classify elderly patients with prostate cancer into three groups: fit, vulnerable, and frail.[18] Screening with such tools and considering not only the age but also health status will be necessary in the future. By using such a screening tool, an individual can be evaluated objectively. Thus, larger prospective studies are required to confirm our findings.

CONCLUSION

In this study, we found that raising the PSA cutoff to 12 ng ml^{-1} for CSPC in elderly individuals can significantly reduce unnecessary prostate biopsies. Therefore, we recommend this CSPC screening plan for elderly men over 75 years of age. By performing this screening, unnecessary biopsies may be reduced and CSPC may be detected efficiently.

AUTHORS CONTRIBUTIONS

HI and KI designed the experiments. HI, SK, TM, RN, and HY collected clinical data. HI, KI, KS, YK, and AM analyzed the data. HI, KI, and AM drafted and revised the manuscript. All authors read and approved the final manuscript

COMPETING INTERESTS

All authors declared no competing interests.

Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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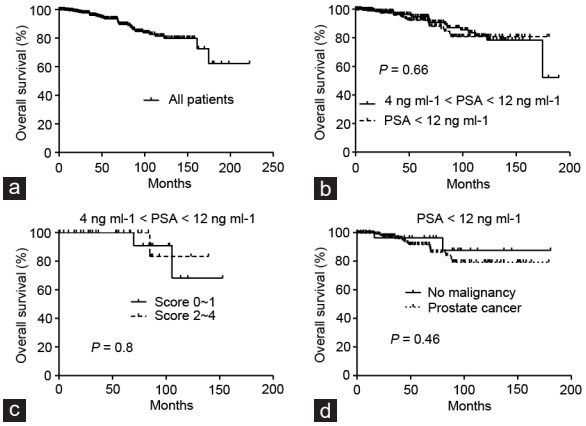

Supplementary Figure 1: OS from prostate biopsy: (**a**) OS in all patients (Median OS: not reached). (**b**) Comparison of OS in 4 ng ml^{-1} ≤ PSA < 12 ng ml^{-1} group and OS in PSA ≥12 ng ml^{-1} group (both median OS: not reached). (**c**) Comparison of OS in score 0~1 group and OS in score 2~4 group in patients with 4 ng ml^{-1} ≤ PSA < 12 ng ml^{-1} (both median OS: not reached). (**d**) Comparison of OS in no malignancy group and OS in prostate cancer group in patients with PSA ≥12 ng ml^{-1} (both median OS: not reached). OS: overall survival; PSA: prostate-specific antigen.