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, Yoshihumi 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 ultrasonography (TRUS) with a 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.³ 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.³ 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.
**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:** 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 years | 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.
Prostate cancer screening in elderly men

H Iwamoto et al

(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\(^{-1}\), 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).

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,

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  |
| 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 = 0.0001). (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.

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 %PSA 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\(^{-1}\) 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.
Asian Journal of Andrology
−1
9–13
presents the CSPC and −1 −1 (−1 14–16 4 CSPC screening algorithm for elderly men over 75 years of age. 3:
and 73.2%, respectively. If the cutoff value is PSA >4 ng ml
increase in the risk of complications.
levels are known to rise with age,
how to manage men aged 70 years and older with elevated PSA. PSA
However, urologists have not yet established a definite consensus on
should be reduced and effectively diagnose CSPC in elderly patients.
For Figure
−1
were 97.2% and 4.8%, respectively,
Figure
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
6
, 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
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
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. HL, 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.
REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019; 69: 7–34.
2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017; 71: 618-29.
3. Daskivich TJ, Fan KH, Koyama T, Albertsen PC, Goodman M, et al. Effect of age, tumor risk, and comorbidity on competing risks for survival in a U.S. population-based cohort of men with prostate cancer. Ann Intern Med 2013; 158: 709–17.
4. Gershman B, Van Housten HK, Herrin J, Moreira DM, Kim SP, et al. Impact of prostate-specific antigen (PSA) screening trials and revised PSA screening guidelines on rates of prostate biopsy and postbiopsy complications. Eur Urol 2017; 71: 55–65.
5. Brawley OW. Trends in prostate cancer in the United States. J Natl Cancer Inst Monogr 2012; 45: 152–6.
6. Graefen M, Schiömm M, Sauter G, Huland H. Detailed quantification of high-grade cancer allows precise prediction of prostate cancer prognosis. Eur Urol 2016; 69: 436–7.
7. Liu ZY, Sun YH, Xu CL, Gao X, Zhang LM, et al. Age-specific PSA reference ranges in Chinese men without prostate cancer. Asian J Androl 2009; 11: 100–3.
8. Oesterling JE, Kumanoto Y, Tsukamoto T, Girman CJ, Guess HA, et al. Serum prostate-specific antigen in a community-based population of healthy Japanese men: lower values than for similarly aged white men. Br J Urol 1995; 75: 347–53.
9. Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol 1992; 147: 815–6.
10. Faria R, Soares MO, Spackman E, Ahmed HU, Brown LC, et al. Optimising the diagnosis of prostate cancer in the era of multiparametric magnetic resonance imaging: a cost-effectiveness analysis based on the prostate MR imaging study (PROMIS). Eur Urol 2018; 73: 23–30.
11. Gosselaar C, Roobol MJ, Roemeling S, Schroder FH. The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol 2008; 54: 581–8.
12. Chen R, Zhou LQ, Cai XB, Xie LP, Huang YR, et al. Percent free prostate-specific antigen is effective to predict prostate biopsy outcome in Chinese men with prostate-specific antigen between 10.1 and 20.0 ng ml⁻¹. Asian J Androl 2015; 17: 1017–21.
13. Tang P, Chen H, Uhlman M, Lin YR, Deng XR, et al. A nomogram based on age, prostate-specific antigen level, prostate volume and digital rectal examination for predicting risk of prostate cancer. Asian J Androl 2013; 15: 129–33.
14. Kott AF, Spaner S, Crump T, Hyndman ME. The role of mpMRI and PSA density in patients with an initial negative prostate biopsy. World J Urol 2018; 36: 201–5.
15. Morses MD, Roman DH, Copetti J, de Santos FS, Agra A, et al. Effects of the addition of quantitative apparent diffusion coefficient data on the diagnostic performance of the PI-RADS v2 scoring system to detect clinically significant prostate cancer. World J Urol 2020; 38: 981–91.
16. Viana PC, Horvat N, do Santos VR, Lima TC, Romao DD, et al. Is possible to rule out clinically significant prostate cancer using PI-RADS v2 for the assessment of prostate MRI? Int Braz J Urol 2019; 45: 724–31.
17. Kenis C, Decoster L, Van Puyvelde K, De Greve J, Conings G, et al. Performance of two geriatric screening tools in older patients with cancer. J Clin Oncol 2014; 32: 19–26.
18. Droz JP, Aapro M, Baldacci L, Boyle H, Van den Broeck T, et al. Management of prostate cancer in older patients: updated recommendations of a working group of the International Society of Geriatric Oncology. Lancet Oncol 2014; 15: e404–14.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

©The Author(s)(2020)
Supplementary Figure 1: OS from prostate biopsy: (a) OS in all patients (Median OS: not reached). (b) Comparison of OS in 4 ng ml$^{-1}$ $\leq$ PSA $<$ 12 ng ml$^{-1}$ group and OS in PSA $\geq$ 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$^{-1}$ $\leq$ 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 $\geq$ 12 ng ml$^{-1}$ (both median OS: not reached). OS: overall survival; PSA: prostate-specific antigen.