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Original Article: Clinical Investigation

Prostate-specific antigen density during dutasteride treatment for 1 year predicts the presence of prostate cancer in benign prostatic hyperplasia after the first negative biopsy (PREDICT study)

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Abbreviations & Acronyms
5ARIs = inhibitors of 5α-reductase
BPH = benign prostatic hyperplasia
CI = confidence interval
DHT = dihydrotestosterone
DRE = digital rectal examination
IPSS = International Prostate Symptom Score
MMP = matrix metalloproteinases
MRI = magnetic resonance imaging
nPC = non-prostate cancer
OR = odds ratio
PC = prostate cancer
PSA = prostate-specific antigen
PSAD = prostate-specific antigen density
QOL = quality of life
ROC = receiver operating characteristic curve
SD = standard deviation

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Objectives: To prospectively evaluate the detection rate of prostate cancer, and to identify the risk factors of prostate cancer detection after a 1-year administration of dutasteride and first negative prostate biopsy.

Methods: Patients with benign prostatic hyperplasia who presented high prostate-specific antigen levels after the first negative prostate biopsy were administered 0.5 mg dutasteride daily for 1 year. They underwent a repeat prostate biopsy after 1 year. The primary end-point was the detection rate of prostate cancer. The secondary end-point was the ability of prostate-specific antigen kinetics to predict prostate cancer detection. Prostate-specific antigen was measured before the initial prostate biopsy and at 6, 9 and 12 months after starting dutasteride. Patients were classified into a prostate cancer and a non-prostate cancer group.

Results: Prostate cancer was detected in 15 of 149 participants (10.1%). The total prostate-specific antigen change between the prostate cancer and non-prostate cancer group at 1 year was significantly different ($P = 0.002$). Although prostate-specific antigen levels at baseline did not significantly differ between study groups ($P = 0.102$), prostate-specific antigen levels at 6, 9 and 12 months were significantly different ($P = 0.002$, $P = 0.001$ and $P < 0.001$, respectively). The mean reduction rate of prostate-specific antigen density between the prostate cancer and non-prostate cancer group at 1 year was significantly different ($-4.25 \pm 76.5\%$ *vs* $-38.0 \pm 28.7\%$, $P = 0.001$). Using a multivariate analysis, a >10% increase of prostate-specific antigen density at 1 year post-dutasteride treatment was the only predictive risk factor for prostate cancer after the first negative prostate biopsy (odds ratio 11.238, 95% confidence interval 3.112–40.577, $P < 0.001$).

Conclusion: In the present study cohort, >10% increase in prostate-specific antigen density represented the only significant predictive risk factor for prostate cancer diagnosis in patients with elevated prostate-specific antigen after the first negative prostate biopsy.

Key words: benign prostatic hyperplasia, dutasteride, high prostate-specific antigen value, negative biopsy, prostate cancer detection.

Introduction

PSA is a useful serum marker for the early detection of prostate cancer. However, an important issue in clinical practice is the mis-sampling of prostate cancer tissue during the initial biopsy.[1] The cancer detection rate in prostate re-biopsy is approximately 15–30% in patients showing a high PSA level after first negative prostate biopsy.[2] The National Comprehensive Cancer Network recommends increasing the minimum PSA velocity of >0.75 ng/mL/year as a criterion for considering prostate re-biopsy.[3,4] Meanwhile, the European Association of Urology guideline recommends the use of MRI before prostate biopsy in patients with prior negative biopsy.[5] However, repeat MRI carries a high cost for some patients, and access to

MRI is limited in some institutions. Therefore, a reliable and brief clinical parameter that indicates a need for repeat biopsy has been established.

5ARIs suppress the potent androgen DHT. Suppression of DHT in the prostate gland by 5ARIs might inhibit the progression of prostate hyperplasia. The PCPT and REDUCE studies provided evidence that 5ARIs reduce the prevalence of prostate cancer compared with a placebo.[6,7] Interestingly, 5ARIs might enhance the predictive value of PSA as a marker for detectable prostate cancer.[8,9] In the REDUCE study, repeat biopsies were taken at 2 and 4 years after dutasteride treatment, along with PSA measurements every 6 months. According to the REDUCE study, dutasteride significantly improved the diagnostic accuracy of prostate cancer and high-grade cancer, as PSA levels at 6 months after dutasteride administration were comparatively increased.[10] However, the detection of prostate cancer and PSA kinetics at 1 year after administering dutasteride remains undefined.

Therefore, we prospectively evaluated the detection rate of prostatic cancer after 1 year of treatment with dutasteride in patients with BPH who presented with elevated PSA levels and a first negative prostate biopsy. We also analyzed predictive risk factors for prostate cancer during the 1-year period after taking dutasteride with the first negative prostate biopsy.

Methods

Study design and patients

The PREDICT study was a prospective multicenter, interventional study in which men received 0.5 mg dutasteride daily for 1 year. We carried out this study between September 2013 and September 2018. The inclusion criteria were as follows: (i) patient age ranging 60–80 years; (ii) negative prostate cancer at initial biopsy; (iii) PSA ≥4 ng/mL before initial biopsy; (iv) BPH with ≥30 mL prostate volume; and (v) ≥8 IPSS. Patients were excluded based on the following criteria: (i) acute prostatitis after initial prostate biopsy; (ii) previous prostate surgery; (iii) prior treatment with drugs that reduce prostate volume, including finasteride, dutasteride, steroid, chlormadinone acetate or allylestrenol; and (iv) a pathological finding of high-grade intra-epithelial neoplasia or atypical small acinar proliferation at the initial prostate biopsy. We also excluded patients whose attending physicians considered that there was high suspicion of prostate cancer based on preoperative MRI and/or DRE, even after negative results were obtained at the initial biopsy (Fig. 1). In addition, we permitted a time lag for repeat biopsy of 3 months before the scheduled 1-year biopsy if PSA levels acutely increased within the first year.

The study design consisted of registered patients receiving 0.5 mg dutasteride daily for 1 year and undergoing a prostate re-biopsy after 1 year of treatment. Daily treatment with 0.5 mg dutasteride started 1 week after the initial biopsy when the outcome of pathological analysis was clarified. The primary end-point was the detection rate of prostate cancer after a 1-year administration of dutasteride. The secondary end-point was the ability of PSA to detect prostate cancer. Serum PSA was measured at 6, 9 and 12 months after the first dutasteride administration. Baseline PSA was designated as the value measured before the initial biopsy. The number of prostate biopsy cores obtained at the initial and repeat biopsies ranged from eight to 14 cores according to the prostate volume (30 ≤ prostate volume < 60 mL; 8–14 cores, ≥60 mL; 12–14 cores) and institution. One or two target biopsies were added if a suspicious area was identified by ultrasound and preoperative MRI. In addition, the same method and number of cores were obtained by transrectal or transperineal ultrasound-guided prostate biopsy at the initial and repeat biopsy. Prostate volume was calculated by using 1.5-T abdominal MRI before each biopsy, because the measurement of transrectal ultrasound-based prostate volume has poor reproducibility by depending on each surgeon. We evaluated the clinical stage using T2- and diffusion-weighted MRI per the subjective judgement of the attending physicians at each institution. Patient data, including age, body mass index, past history, family history, IPSS, PSA value, prostate volume, PSAD, number of biopsied cores, DRE and MRI results, were collected from patient medical records. Positive biopsies were graded using the Gleason scoring system based on the International Society of Urological Pathology grade group in 2014 (International Society of Urological Pathology 2014). We compared these characteristics between the PC and nPC groups. In addition, we established the ROC to determine the cut-off value to distinguish between PC and nPC, and then evaluated the predictive risk factors to detect prostate cancer during the 1-year dutasteride treatment period.

The institutional review board of each participating institution approved the study protocol (UMIN ID; 000010585). Each patient that registered provided written informed consent for this study.

Statistical analysis

We calculated the sample size setting before the study due to plan to compare between PC and nPC groups in the multivariate analysis. We would consider appropriate for four variable factors in the multivariate analysis. Therefore, we calculated that we would need 40 prostate cancer patients. Prostate cancer detection in repeat biopsy when taking dutasteride in the REDUCE study was 19.9%. According to estimating 20% prostate cancer detection in repeat biopsy, we considered 200 available cases over a 4-year period for the multicenter study. Data were analyzed using SPSS software (version 21; IBM Corporation, Armonk, NY, USA). The collected data, including age, body mass index, IPSS, QOL, PSA value, prostate volume, PSAD and PSA change, are presented as the mean value ± SD. Student's *t*-test and Welch's *t*-test were used to compare PC with nPC groups using a mean value for each item. The Youden index for ROC analysis, which was calculated by (sensitivity + specificity − 1), was used to determine the cut-off value. Additionally, a χ^2-test for univariate analysis, stepwise logistics regression analysis and multivariate analysis were used to evaluate the predictive risk factors to detect prostate cancer during the 1-year dutasteride administration period. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Of 203 patients who were registered for the present study, 54 patients were excluded as a result of adverse drug effects

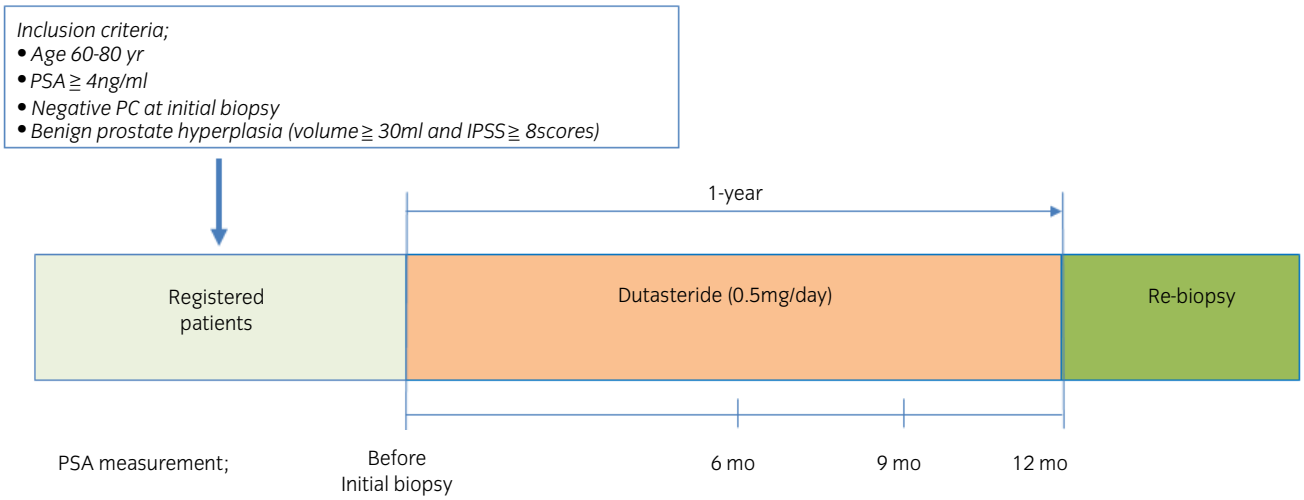

Fig. 1 Study design.

(n = 11), rejected repeat biopsy (n = 24), lost to follow up (n = 5), failed data (n = 3), surgery for hyperplasia (n = 1) and unknown reasons (n = 10). The remaining patients (73.3%) underwent a repeat prostate biopsy after the first administration of dutasteride for 1 year (Fig. 2). The mean age of the cohort was 69.3 ± 5.2 years. The mean initial PSA level at pre-biopsy was 8.5 ± 5.3 ng/mL. The mean prostate volume was 55.2 ± 19.7 mL. The mean number of cores at initial biopsy was 12.0 ± 1.9. Of 149 patients, prostate cancer was detected in 15 patients (10.1%). The distribution of Gleason scores detected in PC was as follows: GS 3 + 3 (5 cases), GS 3 + 4 (3 cases), GS 4 + 3 (6 cases) and GS 4 + 4 (1 case; Table 1). The mean age in the PC group was significantly higher compared with the nPC (72.3 ± 5.2 *vs* 69.4 ± 5.1, P = 0.021). The total PSA change between PC and nPC over a period of 1 year was significantly different (P = 0.0022; Fig. 3). Although the initial PSA value was not significantly different between the PC and nPC group, PSA values at 6, 9 and 12 months were significantly different (P = 0.002, P = 0.001 and P < 0.001, respectively), However, the PSA change from months 9 to 12 was not significantly different between the PC and nPC group (P = 0.061; Fig. 3). The mean reduction rate in PSA for 1 year after taking dutasteride in the PC group was significantly lower compared with the nPC group (−38.8 ± 37.6% *vs* −54.7 ± 20.9%, P = 0.012). Although the mean reduction rate of prostate volume at 1 year was not significantly different between the PC and nPC (−28.8 ± 23.9% *vs* −25.0 ± 17.2, P = 0.446) groups, PSAD at 1 year for the nPC group significantly decreased compared with the PC group (P < 0.001). Furthermore, the mean reduction rate of PSAD at 1 year was significantly different (−4.25 ± 76.5% *vs* −38.0 ± 28.7%, P = 0.001; Table 2). According to ROC analysis, the cut-off value for patient age, PSAD at re-biopsy, the reduction rate of PSA at 1 year and the reduction rate of

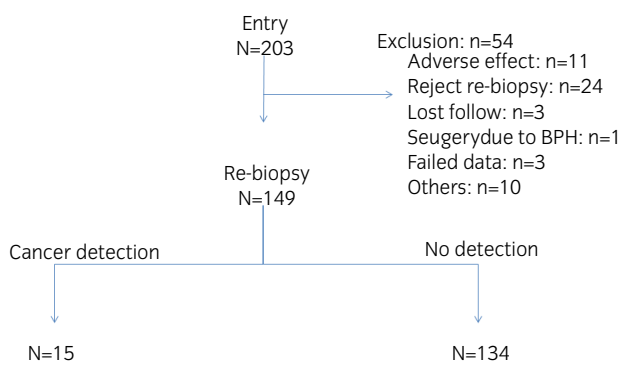

Fig. 2 Flow diagram.

Table 1 Baseline characteristics of the study participants and prostate cancer detection

Characteristic	
Age, years (SD)	69.3 (5.2)
Body mass index, % (SD)	23.5 (3.1)
Family history of prostate cancer, *n* (%)	13 (8.7)
IPSS (SD)	14.8 (6.5)
QOL (SD)	4.2 (1.6)
Pre-biopsy initial – total PSA, ng/mL (SD)	8.5 (5.3)
Prostate volume, mL (SD)	55.2 (19.7)
PSAD, ng/mL·mL (SD)	0.18 (0.16)
Cores at initial biopsy (SD)	12.0 (1.9)
DRE, *n* (%)	
cT1c	133 (89.2)
cT2a	14 (9.4)
cT2c	2 (1.3)
MRI (T2), *n* (%)	
cT1c	102 (68.4)
cT2a	42 (28.1)
cT2c	4 (2.6)
>cT3	1 (0.6)
Prostate cancer detection at re-biopsy, *n* (%)	15 (10.06)
Gleason score, *n* (%)	
3 + 3	5 (3.3)
3 + 4	3 (2.0)
4 + 3	6 (4.0)
4 + 4	1 (0.6)

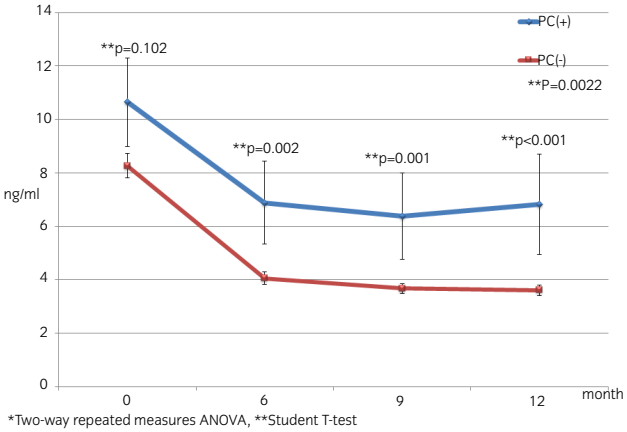

Fig. 3 Change of total PSA by prostate cancer detection. *Two-way repeated measures ANOVA; **Student's *t*-test.

Table 2 Demographics between prostate cancer and non-prostate cancer group

Characteristic	Prostate cancer (n = 15)	Non-prostate cancer (n = 134)	P-value†
Age, years (SD)	72.3 (5.2)	69.4 (5.1)	0.021
Body mass index, % (SD)	23.4 (2.6)	23.5 (3.1)	0.977
Initial – total PSA, ng/mL (SD)	10.6 (6.4)	8.3 (5.2)	0.102
Total PSA after 12 months, ng/mL (SD)	6.82 (7.2)	3.58 (2.1)	<0.001
Reduction rate of PSA after 1 year, % (SD)	−38.8 (37.6)	−54.7 (20.9)	0.012
Prostate volume, mL (SD)			
At pre-biopsy	51.2 (19.5)	55.6 (19.7)	0.412
At re-biopsy	35.7 (16.9)	41.9 (16.4)	0.173
Reduction rate of prostate volume after 1 year, % (SD)	−28.8 (23.9)	−25.0 (17.2)	0.446
PSA density, ng/mL·mL (SD)			
At pre-biopsy	0.22 (0.13)	0.17 (0.16)	0.33
At re-biopsy	0.23 (0.26)	0.09 (0.06)	<0.001
Reduction rate of PSA density after 1 year, % (SD)	−4.25 (76.5)	−38.0 (28.7)	0.001

Total n = 149. †Student's *t*-test, Welch's *t*-test.

PSAD at 1 year to distinguish prostate cancer, were 70 years, 0.11 ng/mL·mL, 40% reduction and 10% increase, respectively (Fig. 4). Using multivariate analysis, more than a 10% increase in PSAD after a 1-year period after receiving dutasteride was the only predictive risk factor for detecting prostate cancer after one negative biopsy (OR 11.238, 95% CI 3.112–40.577, P = 0.0002; Table 3).

Discussion

In the present study, we found that a >10% increase in PSAD at 1 year of dutasteride treatment was the best clinical indicator to detect prostate cancer in repeat biopsy. Some urologists have hypothesized that prostate cancer is easier to detect in smaller prostate glands than larger prostate glands, and then, theoretically, tumors in larger prostate glands are more susceptible to underdetection due to inadequate sampling.[11] Some studies found that dutasteride treatment also reduced total prostate volume by 26% at 24 months and 27.3% at 48 months for BPH.[12,13] Therefore, a reduction in prostate gland volume might improve prostate cancer detection in men receiving dutasteride.[14]

In the present study, the prostate volume showed a decrease from the baseline after 1 year of dutasteride therapy. Although the reduction rate of prostate volume with men taking dutasteride between the PC and nPC groups for 1 year was 28.8% and 25.0%, respectively, which was not significantly different, the PSA value in the nPC group significantly decreased in comparison with the PC group after 1 year of dutasteride therapy. Therefore, we described PSAD kinetics for 1 year from the point of view of variation in the PSA level and the prostate volume between the PC and nPC groups. In the present study, PSAD levels after 1 year in the nPC group significantly decreased compared with the PC group (P < 0.001). Furthermore, the mean reduction rate of PSAD at 1 year was significantly different between the two groups.

Moros *et al*. investigated whether finasteride might attenuate tumor aggressiveness and invasion through MMP2 and MMP9 downregulation, which could vary depending on the androgen responsiveness of a patient's prostate cells.[15] Therefore, we hypothesized that dutasteride also might have some features that exert a weak suppression effect on the portion with cancer cells, but manifest a significant suppression in the portion of prostate tissue without cancer cells. Therefore, when considering prostate cancer in the prostate gland, PSA might remain at a high level compared with no prostate cancer, even if the prostate volume is reduced. Consequently, we guess that PSAD in patients with prostate cancer is kept at a high value after 1 year of dutasteride treatment.

The interpretation of PSA kinetics requires meticulous attention, as the PSA value decreases by 50% when taking dutasteride for 6 months. Therefore, the parameters that determine whether to undergo the repeat prostate biopsy in men taking dutasteride were not consistent. Some investigators found that persistent PSA rising from PSA nadir and more than two increases after 6 months of dutasteride therapy should be an indicator for repeat biopsy.[16,17] In addition, Andriole *et al*.[18] determined that the optimal combination of sensitivity and specificity was achieved with a PSA increase of 0.8 ng/mL as the threshold for prostate biopsy in patients using dutasteride from the REDUCE study. To our knowledge, there are no reports that describe PSAD kinetics with dutasteride as a potential indicator for detecting prostate cancer in repeat biopsies.

In a subanalysis of the REDUCE study regarding PSA kinetics, for men treated with dutasteride having no tumor or low-grade cancer (Gleason score 5–6), the serum PSA level at 6 months tends to decrease or remain stable over time.[19–21] In the present study, the total PSA change between the PC and nPC groups over a period of 1 year was significantly different. Specifically, PSA levels in the nPC group continuously decreased during the 1-year period of dutasteride therapy.

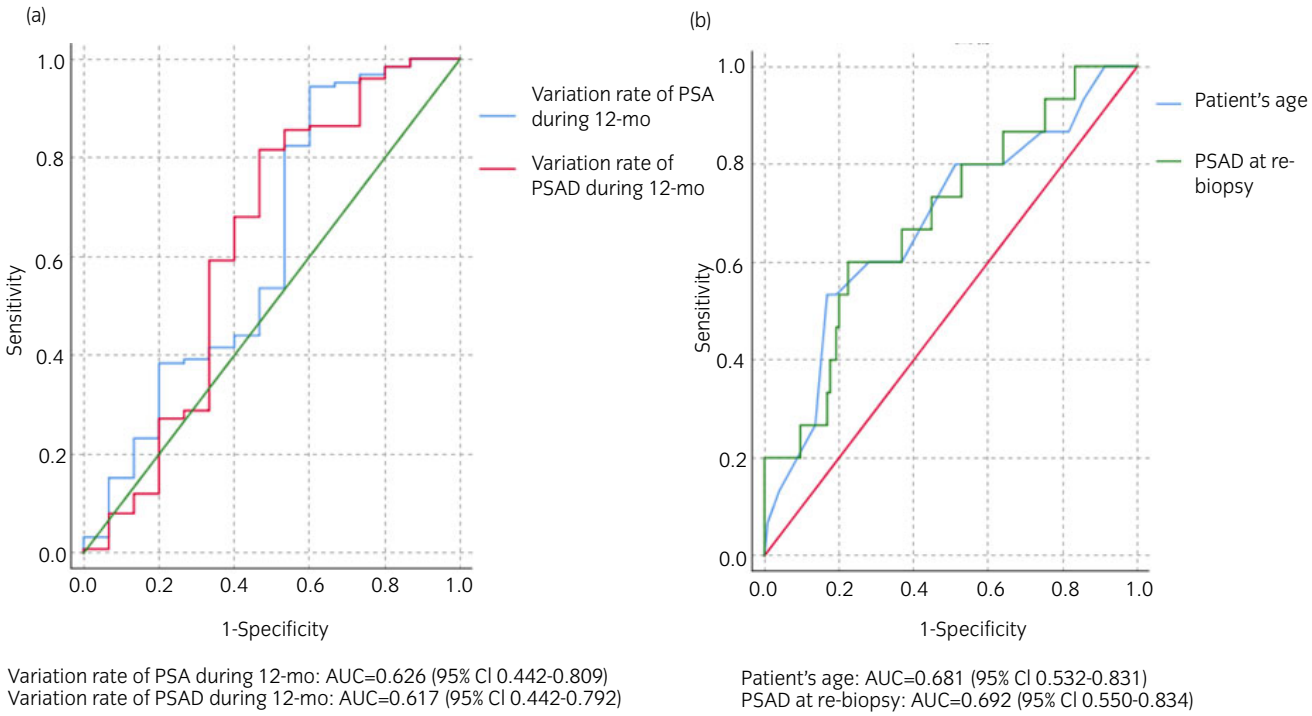

Fig. 4 ROC curve analysis to determine the cut-off value for distinguishing prostate cancer. (a) The ROC of the reduction rate of PSA and reduction rate of PSAD during the 1-year period. (b) The ROC of patient's age and PSAD at re-biopsy.

Table 3 Predictive risk factors for prostate cancer detection after 1-year administration of dutasteride

Characteristic	Univariate analysis†	Multivariate analysis‡
Age (<70 years or not)	0.034	
Reduction rate of PSA during 1 year (<40% reduction or not)	0.006	
PSAD at re-biopsy (<0.11 or not)	0.037	
Reduction rate of PSAD during 1 year (>10% increase or not)	<0.001	OR 11.238 (95% CI 3.112–40.577, P = 0.0002)

Total n = 149. †χ^2-test. ‡Logistics regression stepwise.

Conversely, the PSA level rose from months 9 to 12 after administration of dutasteride in PC, but was not significantly different. However, this information is inadequate to assess the effect of 1-year dutasteride treatment, as the number of patients who were diagnosed with prostate cancer was insufficient in the present study. Regardless, the continuous decrease of PSA levels in the nPC group over a period of 1 year, similar to the findings of the REDUCE study, might represent an effective variable for predicting the presence of prostate cancer.

Kaplan *et al*. reported that patients diagnosed with prostate cancer after 1 year of finasteride treatment had a smaller decrease in PSA compared with those in whom prostate cancer did not develop.[22] Heo *et al*. reported a significant difference in the percentage change of PSA at 6 months of 5ARIs treatment from the initial level in men with and without prostate cancer (29.1% *vs* 34.2%).[17] Kravchick *et al*. found that PSA decreased to 26.73% in patients with cancer, compared with 40.54% in patients without cancer after 6 months of dutasteride therapy.[23] Furthermore, they concluded that a PSA decline of <40% should be considered as an indicator for repeat biopsy. In the present study, a reduction of PSA in the PC group for 1 year after taking dutasteride was significantly lower compared with that of the nPC group. Furthermore, patients with a PSA reduction of <40% during a 1-year period showed significantly higher detectable prostate cancer in univariate analysis, but there was not a significant difference in multivariate analysis.

Furthermore, we investigated the detection of prostate cancer with dutasteride treatment and PSA kinetics in the Japanese population, for whom there have previously been quite few reports. It is well known that the incidence of prostate cancer varies worldwide, with higher rates found in North America and Europe, whereas lower rates are observed in Asia.[24] In addition, the prostate volume in Japanese men is lower than in white men.[25] Therefore, there might be racial specificity on the prostate gland. Akaza *et al*. reported the efficiency and safety of dutasteride on prostate cancer risk in 57 Japanese men from the REDUCE study data. According to this report, among Japanese men, the incidence of prostate cancer in dutasteride-treated men was lower, at 8.3%, than that of placebo-treated men, at 21.4%. However, they did not mention PSA kinetics in Japanese men. The present study found not only prostate cancer detection in dutasteride-treated men, but also PSA kinetics in 149 Japanese men.

The present study had several limitations. First, this prospective cohort study had a relatively small number of participants. Second, the number of participants diagnosed with prostate

cancer in this study was also small. However, this study remains interesting and important with respect to the short-term PSA kinetics in Japanese men treated with dutasteride. Third, we included and evaluated patients with both clinically significant (Gleason score 7) and clinically insignificant (Gleason score 6) prostate cancer in the present study. However, the evaluation of PSA kinetics in patients with Gleason scores >7 might be sufficient in clinical practice. Fourth, we carried out two methods of prostate biopsy; namely, transperitoneal and transrectal biopsy, depending on the hospital in this study, and we did not utilize current MRI–ultrasound fusion biopsy, because this novel system was not consistently available in Japan when our present study was started. Therefore, we added one or two target biopsies based on preoperative MRI and intraoperative ultrasound in each institution. Fifth, we included some patients with cT2a or greater based on preoperative MRI and/or DRE because of the initial negative biopsy and lower consideration of a high suspicion of prostate cancer per the judgement of each attending physician. However, there are some issues if patients with cT2a or greater based on preoperative MRI and/or DRE are included or not.

Anyhow, the variation of PSAD might represent a meaningful indicator to recommend a repeat prostate biopsy for patients taking dutasteride for a 1-year period in the Japanese population.

In conclusion, more than a 10% increase in PSAD for 1 year after first dutasteride treatment might be the only predictive risk factor for prostate cancer detection in repeat prostate biopsy. Repeat biopsy might be recommended when PSAD increases after 1 year.

Acknowledgments

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Conflict of interest

None declared.

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