

Original Article

Oral administration of cernitin pollen extract (Cernilton®) for 30 days might be useful to avoid unnecessary biopsy in prostate biopsy candidates: A preliminary study

Yoshikazu Togo,¹ Daishi Ichioka,² Jun Miyazaki,² Yoshiko Maeda,³ Koji Kameyama,⁴ Mitsuru Yasuda,⁴ Yoshiki Hiyama,⁵ Satoshi Takahashi,⁶ Hiroshi Nagae,⁷ Seiichi Hirota⁸ and Shingo Yamamoto,¹ on behalf of the Japanese Research Group for Urinary Tract Infection (JRGU)

¹Department of Urology, Hyogo College of Medicine, Nishinomiya, Hyogo, ²Department of Urology, Faculty of Medicine, University of Tsukuba, Tsukuba, ³Department of Urology, Showa University School of Medicine, Tokyo, ⁴Department of Urology, Gifu University Hospital, Gifu, ⁵Department of Urology, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, ⁶Department of Infection Control and Laboratory Medicine, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, ⁷Nagae Prostate-care Clinic, Hamamatsu, Shizuoka, and ⁸Department of Pathology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

Abbreviation & Acronyms

DRE = digital rectal examination
IPSS = International Prostate Symptom Score
MRI = magnetic resonance imaging
NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index
PSA = prostate-specific antigen

Correspondence: Yoshikazu Togo M.D., Ph.D., Department of Urology, Hyogo College of Medicine, 1-1 Mukogawacho, Nishinomiya, Hyogo 663-8501, Japan. Email: ytogohg@gmail.com

Received 20 July 2017;
accepted 29 January 2018.

Objectives: To assess the effect of cernitin pollen extract on serum prostate-specific antigen level prostate biopsy candidates, and to develop an ideal protocol to avoid an unnecessary biopsy procedure.

Methods: A total of 61 patients were administered cernitin pollen extract tablets (two tablets t.i.d.) for 30 days, and then underwent a prostate biopsy with ≥ 12 systematic and targeted biopsy cores obtained. Serum prostate-specific antigen levels were examined before and after administration of the pollen extract, and the change in serum prostate-specific antigen and the rate of change were analyzed in relation to negative and positive biopsy results for cancer.

Results: The mean change in serum prostate-specific antigen and rate of change after administration of cernitin pollen extract in all patients were -0.6 ± 1.4 ng/mL and $-7.6 \pm 16.1\%$, respectively, which were significantly different from the baseline values ($P = 0.0003$ and $P = 0.0005$, respectively). When prostate-specific antigen change values and rates were compared between patients negative and positive for cancer, a significant difference between those groups was observed ($P = 0.04$ and $P = 0.03$, respectively).

Conclusions: The present study is the first to show that an ideal protocol using cernitin pollen extract has the potential to avoid an unnecessary prostate biopsy procedure in patients with elevated prostate-specific antigen, possibly caused by inflammation. Additional studies with greater numbers of participants are required to confirm our findings and develop an ideal protocol.

Key words: cernitin pollen extract, chronic prostatitis, prostate biopsy, prostate cancer, prostate-specific antigen.

Introduction

A prostate biopsy is an indispensable procedure for the diagnosis of prostate cancer. Although a high serum PSA level indicates the possibility of prostate cancer, it has a low positive predictive rate of approximately 25% in patients with a standard or higher PSA level,^{1,2} while various complications can occur from a biopsy procedure, such as severe bleeding, urinary irritability and febrile infection.³ Therefore, it is important to select candidates with high specificity for detection of prostate cancer in order to avoid an unnecessary procedure.

Chronic inflammation in the prostate can cause a rise in serum PSA level, and it has been reported that it is possible to avoid an unnecessary biopsy in such patients by giving an administration of fluoroquinolone for 2–4 weeks to reduce that level.^{4–7} However, long-term administration of antibiotics given to prostate biopsy candidates is disadvantageous from the

standpoint of collateral damage, as well as medical economics. Thus, such antimicrobial use is not recommended as a routine procedure.

In the European Association of Urology guidelines, phytotherapy including cernitin pollen extract (Cernilton®) is recommended for patients with inflammatory prostate pain syndrome,⁸ with no known reports of severe adverse events associated with its administration.^{9–11} If such a non-antimicrobial drug can effectively reduce serum PSA in prostate biopsy candidates with chronic inflammation of the prostate, an optimal method including that could be developed for avoidance of an unnecessary biopsy. To assess the effect of cernitin pollen extract on serum PSA, we administered it orally to prostate biopsy candidates for 30 days before carrying out a prostate biopsy procedure, then prospectively investigated the relationship between reduction in serum PSA level and prostate biopsy outcome.

Methods

The present prospective multicenter study was carried out at six institutions from January 2014 to December 2016. Patients with high serum PSA and scheduled for a prostate biopsy were recruited, with voluntary written informed consent obtained from each prior to enrollment. Enrolled patients were administered cernitin pollen extract tablets (two tablets t.i.d.) for 30 days, then underwent a transperineal or transrectal prostate biopsy procedure, with ≥ 12 random and targeted cores obtained. Serum PSA level was examined before and after administration of the extract. Inclusion criteria were: (i) men aged ≥ 40 years; (ii) initial biopsy; (iii) serum PSA level between 4 and 20 ng/mL; and (iv) negative digital rectal examination findings. Exclusion criteria included: (i) genitourinary tract infection within 3 months; (ii) presently suffering from another malignancy; (iii) indwelling urethral or ureteral catheter; (iv) post-void residual urine volume ≥ 100 mL; (v) antimicrobial use within 3 months; and (vi) use of drugs within the previous 1 year that might affect the serum PSA level, such as cernitin pollen extract, 5 α -reductase inhibitor, chlormadinone acetate and allylestrenol. The inclusion and exclusion criteria used are shown in Table 1.

The primary aim of the present study was to examine the change in serum PSA level after administration of cernitin pollen extract in patients shown to be positive or negative for cancer in prostate biopsy findings. Although imaging results were not considered because of the enrollment criteria, PSA change was also analyzed in association with positive and negative MRI findings in some patients. In addition, we assessed NIH-CPSI and IPSS scores before and after oral administration of cernitin pollen extract to compare between patients found positive and those found negative for cancer in the prostate biopsy results. Using histological findings, we also investigated the grade of inflammation in prostatic tissue (1: mild, 2: moderate, 3: severe) according to the classification proposed by Nickel *et al.*,¹² and then compared between subgroups divided by positivity for cancer and change in PSA.

The present study was approved by the ethics committee of each participating institution, including Hyogo College of

Table 1 Inclusion and exclusion criteria

Inclusion criteria	
Age	≥ 40 years
Initial biopsy	
PSA	4–20 ng/mL
Negative DRE	
Exclusion criteria	
Genitourinary tract infection	within 3 months
Other malignancy	
Indwelling urethral or ureteral catheter	
PVR	≥ 100 mL
Antimicrobial use	within 3 months
Use of drug within 1 year that might affect serum PSA level, such as cernitin pollen extract, 5 α -reductase inhibitor, chlormadinone acetate, allylestrenol	

Medicine (approval #1610), and has been registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: UMIN000017593).

Statistical analysis

Comparisons between groups and associations between categorical variables were analyzed by a Wilcoxon signed-rank test and Mann–Whitney *U*-test. *P*-values < 0.05 were considered to be significant.

Results

Of the 78 patients recruited, 17 were excluded (nine repeat biopsy, two PSA > 20 ng/mL, two no PSA examination after administration of cernitin pollen extract, one insufficient administration of cernitin pollen extract, one positive digital rectal examination, one taking dutasteride, one unknown hematuria), thus 61 were enrolled and subjected to the present analyses (Fig. 1). Patient background information is shown in Table 2. Of the 61 analyzed, 25 (41.0%) were positive and 36 (59.0%) were negative for cancer in prostate biopsy findings. Among those negative for cancer, one underwent a repeated biopsy, though no cancer was detected in any during the follow-up period (median 29.4 months, range 19–43 months) after the prostate biopsy procedure. The change in serum PSA level and rate of change after administration of cernitin pollen extract in all patients were -0.6 ± 1.4 ng/mL and $-7.6 \pm 16.1\%$, respectively, which were significantly different ($P = 0.0003$ and $P = 0.0005$, respectively) as compared with before administration (Fig. 2). As for patients negative for cancer in prostate biopsy findings ($n = 36$), those values were -0.9 ± 1.7 ng/mL and $-10.5 \pm 17.6\%$, respectively, with each showing a significant difference ($P = 0.001$ and $P = 0.001$, respectively). In contrast, for patients positive for cancer ($n = 25$), the difference in those values between before and after administration (-0.3 ± 1.0 ng/mL and $-3.7 \pm 13.0\%$, respectively) were not significantly different ($P = 0.08$ and $P = 0.17$, respectively; Table 3). When the change in PSA level and rate of change were compared between patients negative and positive

for cancer, significant differences were observed ($P = 0.04$ and $P = 0.03$, respectively; Fig. 3).

We also analyzed the group of patients who had negative findings in MRI carried out before undergoing the prostate biopsy procedure ($n = 27$). In a comparison between those patients shown negative and positive for cancer in the biopsy findings, the change in PSA level and rate of change were again significantly different ($P = 0.02$ and $P = 0.04$, respectively; Fig. 4a). In contrast, in patients with positive findings shown by MRI before the prostate biopsy ($n = 32$), there were no significant differences for those values between patients negative and positive for cancer in prostate biopsy results ($P = 0.18$ and $P = 0.15$, respectively; Fig. 4b).

Among the 61 patients analyzed, 44 showed a decline in PSA level, of whom 16 (36.4%) were positive for cancer in prostate biopsy results. In contrast, 17 showed an elevation of PSA level, of whom nine (52.9%) had positive biopsy results. Of the 20 patients with a PSA decline of ≥ 1 ng/mL from the baseline measurement, five (25.0%) had cancer detected in the prostate biopsy examination, whereas only one (14.3%) of seven with a decline of ≥ 2 ng/mL had cancer detected by prostate biopsy results. Four patients had a decline of ≥ 3 ng/mL and none had cancer detected (Fig. 5). There was no correlation between Gleason sum score and PSA decline.

The mean values for NIH-CPSI total, pain, urinary and quality of life domain scores at baseline were 8.3 ± 5.8 , 1.6 ± 2.9 , 2.5 ± 2.2 and 4.2 ± 2.7 , respectively, whereas those after administration of cernitin pollen extract were 8.8 ± 5.8 , 1.4 ± 2.2 , 2.9 ± 2.4 and 4.5 ± 3.1 , respectively, which were not significantly different from the baseline values ($P = 0.32$, 0.93 , 0.08 and 0.30 , respectively). Furthermore, the mean IPSS total, voiding symptom, storage symptom and quality of life scores at baseline were 10.6 ± 7.4 , 6.3 ± 5.3 , 4.2 ± 3.0 and 3.0 ± 1.5 , respectively, whereas those were 9.6 ± 5.9 , 5.6 ± 4.3 , 4.0 ± 2.8 and 2.8 ± 1.6 , respectively, after receiving the cernitin pollen extract, with no significant differences seen between before and after administration ($P = 0.11$, 0.08 , 0.89 and 0.19 , respectively).

Prostate biopsy specimens from 60 of the 61 patients were examined to determine the inflammatory infiltrate grade. There was no significant difference found between patients negative ($n = 35$) and positive for cancer ($n = 25$; 2.1 ± 0.8 vs 1.9 ± 0.9 ; $P = 0.23$), or between patients with ($n = 43$) and without ($n = 17$) a decline in PSA level (2.0 ± 0.8 vs 1.9 ± 1.0 ; $P = 0.61$).

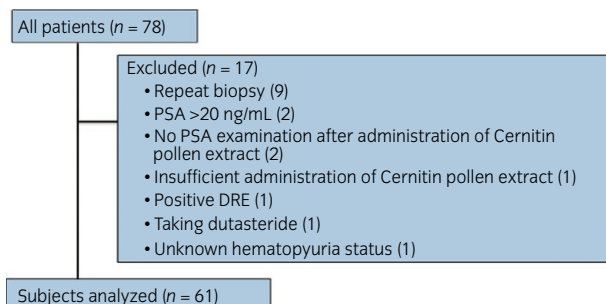


Fig. 1 Flowchart of patient selection in the present study.

Table 2 Background of patients

Characteristics	Mean \pm SD	Range
Age (years)	67.8 \pm 7.1	42–80
PSA (ng/mL)	8.0 \pm 3.6	4.1–19.4
Prostate volume (mL)	35.9 \pm 19.8	8–121.4
IPSS	10.6 \pm 7.4	0–29
NIH-CPSI	8.3 \pm 5.8	0–21

Discussion

A prostatic biopsy procedure is indispensable for detection of prostate cancer, though it might be accompanied by complications. In addition, with the recent increase in resistant bacteria, fatal infective complications including bacteremia after such a procedure have been reported.^{13,14} Therefore, in order to select proper candidate patients for a prostate biopsy, PSA-related parameters, such as free/total PSA ratio,¹⁵ PSA velocity¹⁶ and PSA density,¹⁷ have been proposed as useful, though each is considered insufficient in regard to specificity.

The level of PSA in serum can rise from inflammation of the prostate caused by conditions other than cancer, with histological chronic inflammation reported to be present in the prostate gland in 29.9–77.6% of patients with benign prostatic hypertrophy.^{18–20} Also, several studies have reported that an unnecessary prostate biopsy procedure can be avoided when a decline in serum PSA level is observed after administration of fluoroquinolone for 2–4 weeks in candidates for the procedure.^{4–7} In contrast, others found no such effect from antimicrobial administration in their patients with a PSA level considered to be in the so-called gray zone.^{21–23} Furthermore, quinolone-resistant *Escherichia coli* bacterial infection induced by a long-term administration of fluoroquinolone has been reported to be a risk factor for sepsis after a prostate biopsy, indicating that antimicrobials should not be routinely administered to candidates for that procedure.^{24,25}

Cernitin pollen extract is considered to be therapeutically effective for chronic prostatitis.⁸ In an *in vitro* study that included basal experiments, that extract induced apoptosis of inflammatory cells and significantly suppressed interstitial hyperplasia, as compared with the control group,²⁶ whereas another reported that it suppressed inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- α .²⁷ With this background in mind, we carried out the present prospective study to assess the influence of cernitin pollen extract, a non-antimicrobial agent, on serum PSA level in prostate biopsy candidates for development of a protocol useful to avoid an unnecessary biopsy procedure.

In the present 61 patients, serum PSA was decreased from the baseline in 44 (72.1%) after administration of cernitin pollen extract, while previous studies have reported declines in serum PSA levels ranging from 59.6–80.3% with the use of antimicrobials.^{4,6,7,21} Furthermore, the mean change in serum PSA level from the baseline for all of our patients was -0.6 ± 1.4 ng/mL, with similar findings (-0.68 to -2.97 ng/mL) reported after antimicrobial administration.^{5,7,21,23}

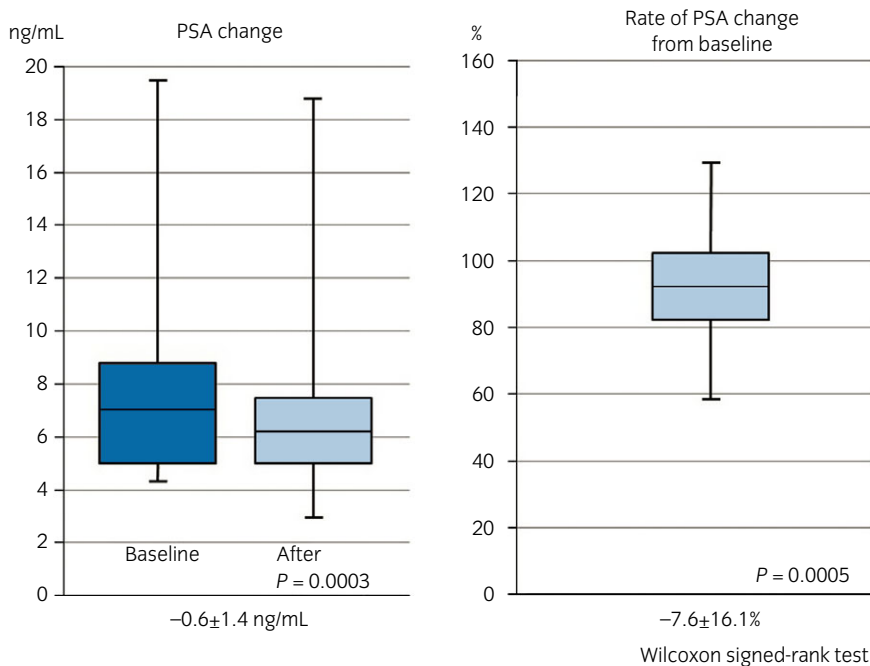


Fig. 2 PSA level change and rate of change after administration of cernitin pollen extract in all patients.

Table 3 Change in PSA level and rate of change after administration of cernitin pollen extract in association with prostate biopsy result

Result of biopsy	Administration of cernitin pollen extract		Change (ng/mL)	P	Rate of change (%)	P
	Before (ng/mL)	After (ng/mL)				
Cancer negative	7.8 ± 3.3 (4.1–18.7)	6.9 ± 3.1 (3.7–18.5)	-0.9 ± 1.7	0.001	-10.5 ± 17.6	0.001
Cancer positive	8.2 ± 3.9 (4.6–19.4)	7.9 ± 4.1 (3.8–18.7)	-0.3 ± 1.0	0.08	-3.7 ± 13.0	0.17

Wilcoxon signed-rank test.

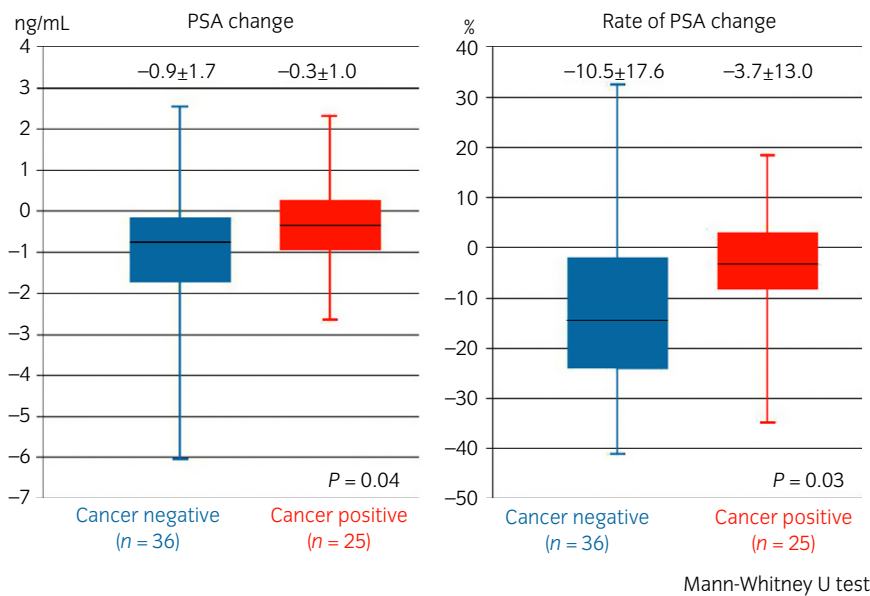


Fig. 3 PSA level change and rate of change after administration of cernitin pollen extract in patients negative (blue rectangle) and positive (red rectangle) for cancer in prostate biopsy findings.

An important finding in the present study is that the change in serum PSA level was significantly greater in patients shown negative for cancer based on biopsy results as

compared with those shown positive. Also, in patients who had negative MRI findings before the prostate biopsy, the changes in PSA level and rate were significantly different

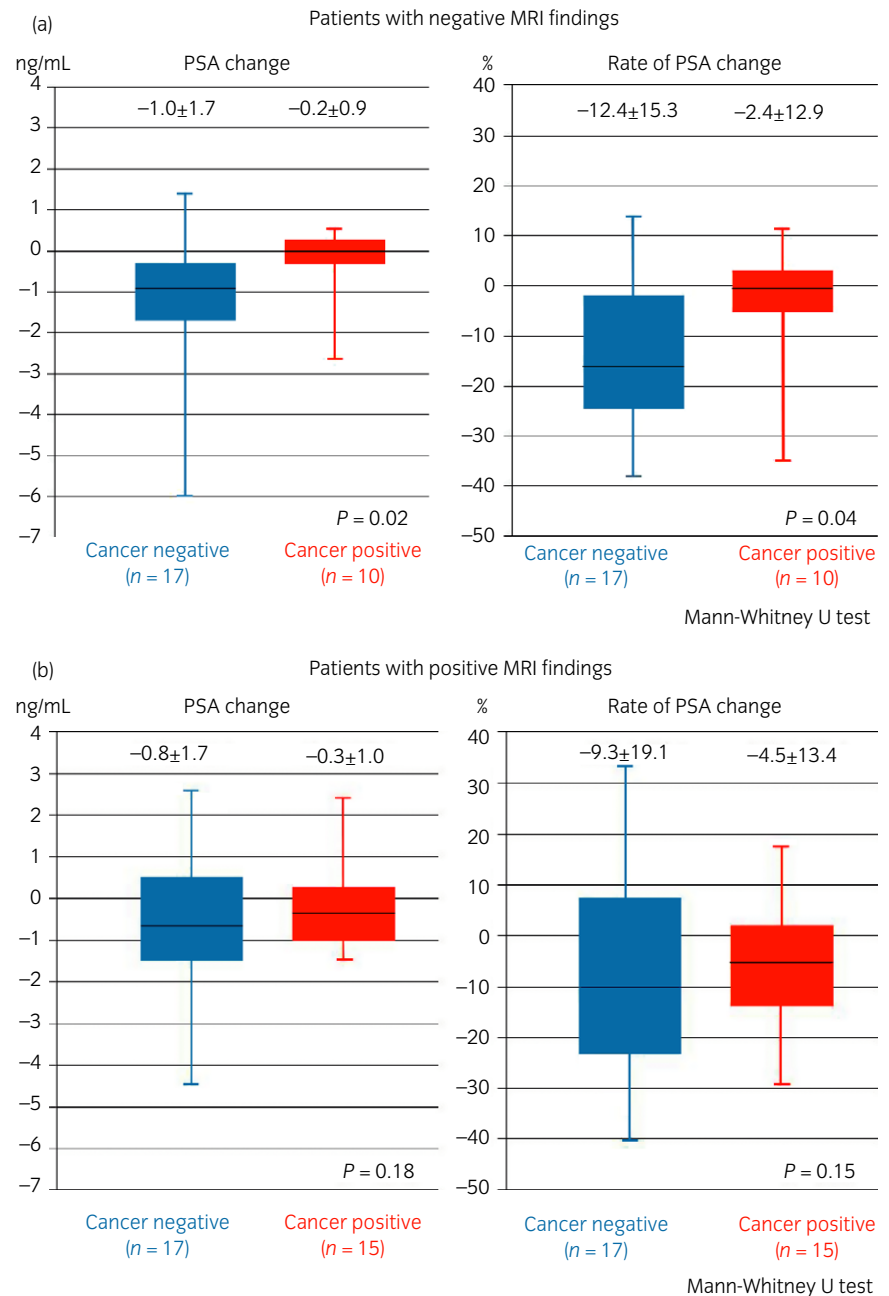


Fig. 4 PSA level change and rate of change after administration of cernitin pollen extract in patients found negative and positive for cancer in prostate biopsy findings. (a) Negative in MRI findings. (b) Positive in MRI findings (blue rectangle: negative for cancer in prostate biopsy findings, red rectangle: positive for cancer in prostate biopsy findings).

between those shown negative and positive for cancer by the biopsy examination, whereas no such difference was observed for patients with positive MRI findings. These results suggest that the present protocol is more useful for patients with negative MRI findings.

Of the 61 patients, 44 had a decline in PSA level after administration of cernitin pollen extract, of whom 16 (36.4%) were positive for cancer in prostate biopsy findings. When we divided those with reduced PSA level into groups with a decline of 1–2, 2–3 and >3 ng/mL from the baseline, cancer was detected in 25%, 14.3% and 0%, respectively, by the prostate biopsy examination, suggesting that a larger decline in that value predicts a higher possibility of negative for cancer. In area under the curve analysis, when the cut-off value

was set at 2 ng/mL of PSA decline, the area under the curve was 0.625 ($P = 0.126$) with a sensitivity of 85.7% and specificity of 44.4%, though a greater number of patients would be required to determine the optimal cut-off value (Fig. 6).

Although a high serum PSA level indicates the possibility of prostate cancer, it has a low positive predictive rate of approximately 25% in patients with a standard or higher PSA level,^{1,2} as Carroll *et al.* reported that the detection rate of prostate cancer is 30–35% and >67% in patients with a PSA level of 4–10 ng/mL and ≥ 10 ng/mL, respectively.²⁸ We also generally believe that a biopsy is necessary for patients with a PSA level of ≥ 10 ng/mL, we consider postponement of the procedure when the PSA level declines into the gray zone after administration of cernitin pollen extract in patients

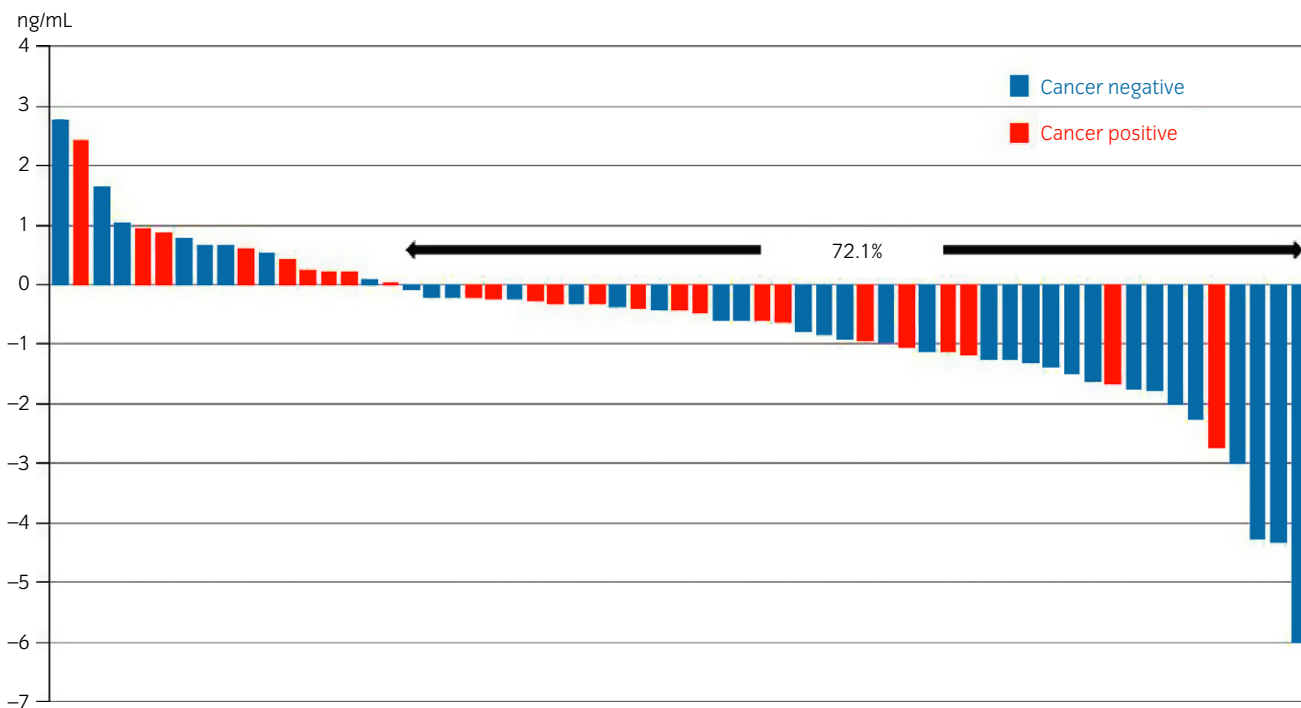


Fig. 5 Waterfall plots showing change in PSA level in all patients.

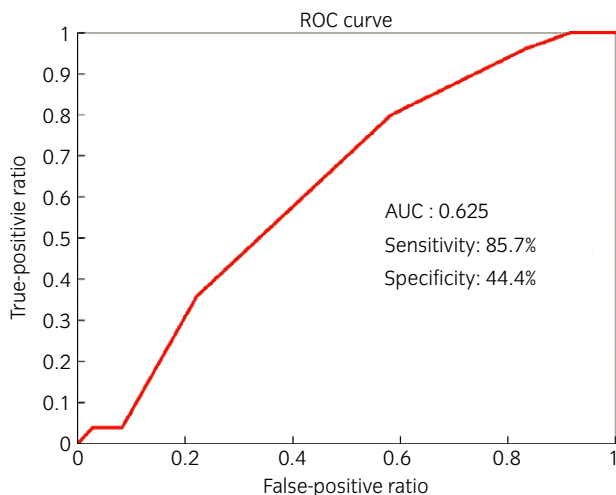


Fig. 6 Receiver operating characteristic curve with cut-off value for PSA decline set at 2 ng/mL.

without positive findings shown in a digital rectal examination and by MRI. We believe that such patients are also good candidates for the present protocol. In the present study, of the 12 patients with a baseline PSA level of ≥ 10 ng/mL, three had a PSA decrease of at least 2 ng/mL by administration of cernitin pollen extract and cancer was found in none of those.

Wagenlehner *et al.* reported that a 12-week administration of cernitin pollen extract in chronic prostatitis/chronic pelvic pain syndrome patients significantly reduced NIH-CPSI total and pain domain scores as compared with a placebo (-8.72 vs -4.77 , $P = 0.0003$; and -4.93 vs -2.79 , $P = 0.0009$;

respectively).⁹ Although we examined changes in CPSI scores before and after administration of that extract, no significant difference was observed, possibly because our patients were candidates for a prostate biopsy procedure, and not suffering from chronic prostatitis or pelvic pain syndrome. Other reports have noted that IPSS was significantly decreased in chronic prostatitis/chronic pelvic pain syndrome patients after a 3-month administration of cernitin pollen extract.^{9,29} Again, no such finding was obtained in the present study, possibly for the same reason noted above.

We also compared the inflammatory infiltrate grade of prostatic tissues between patients negative and positive for cancer, as well as between patients with and without a decline in PSA level. Although we speculated that the grade of inflammation would be higher in patients negative for cancer or with higher PSA levels, no significant difference was found between those subgroups, possibly because we investigated prostatic tissue inflammation only after histological modification by administration of cernitin pollen extract. A future study is required to examine the correlation between PSA change and change of inflammation of prostatic tissue shown by histological grade before and after administration of this pollen extract.

The present findings are limited by the low number of patients and lack of randomization, thus a randomized controlled trial with a greater number of patients is required to develop a nomogram for the prediction of prostate cancer with use of the present protocol.

This is the first report of the use of cernitin pollen extract as part of a possible ideal protocol to avoid an unnecessary prostate biopsy procedure in patients with high PSA levels, possibly caused by inflammation. In the present preliminary study, the extract was administered for only 30 days before

carrying out a prostate biopsy, because it would be unethical for those with a high PSA level to be asked to wait for a longer period, even though a longer administration period might be more effective.

Acknowledgments

The authors express their sincere appreciation to the urologists and their colleagues at the participating institutions for cooperation with this study.

Conflict of interest

None declared.

References

- Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. *J. Am. Board Fam. Pract.* 2003; **16**: 95–101.
- Schröder FH, Hugosson J, Roobol MJ *et al.* ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. *N. Engl. J. Med.* 2009; **360**: 1320–8.
- Loeb S, Vellekoop A, Ahmed HU *et al.* Systematic review of complication of prostate biopsy. *Eur. Urol.* 2013; **64**: 876–92.
- Karazanashvili G, Managadze L. Prostate-specific antigen (PSA) values change after antibacterial therapy of prostate inflammation, as a diagnostic method for prostate cancer screening in cases of PSA values within 4–10 ng/mL and nonsuspicious results of digital rectal examination. *Eur. Urol.* 2001; **39**: 538–43.
- Schaeffer AJ, Wu SC, Tennenberg AM, Kahn JB. Treatment of chronic bacterial prostatitis with levofloxacin and ciprofloxacin lowers serum prostate specific antigen. *J. Urol.* 2005; **174**: 161–4.
- Serretta V, Catanese A, Daricello G *et al.* PSA reduction (after antibiotics) permits to avoid or postpone prostate biopsy in selected patients. *Prostate. Cancer. Prostatic. Dis.* 2008; **11**: 148–52.
- Kobayashi M, Nukui A, Morita T. Serum PSA and percent free PSA values changes after antibiotic treatment. A diagnostic method in prostate cancer suspects with asymptomatic prostatitis. *Urol. Int.* 2008; **80**: 186–92.
- Engeler D, Baranowski AP, Borovicka J *et al.* Guidelines on chronic pelvic pain. 2014. [Cited 15 Mar 2018.] Available from URL: https://uroweb.org/wp-content/uploads/26-Chronic-Pelvic-Pain_LR.pdf.
- Wagenlehner FME, Schneider H, Ludwig M, Schnitker J, Brähler E, Weidner W. A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis–chronic pelvic pain syndrome: a multicentre, randomised, prospective, double-blind, placebo-controlled phase 3 study. *Eur. Urol.* 2009; **56**: 544–51.
- Iwamura H, Koie T, Soma O *et al.* Eviprostat has an identical effect compared to pollen extract (Cernilton) in patients with chronic prostatitis/chronic pelvic pain syndrome: a randomized, prospective study. *BMC. Urol.* 2015; **15**: 120.
- Cai T, Luciani LG, Caola I *et al.* Effects of pollen extract in association with vitamins (DEPROX 500[®]) for pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome: results from a pilot study. *Urologia.* 2013; **80**(Suppl 22): 5–10.
- Nickel JC, True LD, Krieger JN, Berger RE, Boag AH, Young ID. Consensus development of a histopathological classification system for chronic prostatic inflammation. *BJU Int.* 2001; **87**: 797–805.
- Williamson DA, Barrett LK, Rogers BA, Freeman JT, Hadway P, Paterson DL. Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant *Escherichia coli*. *Clin. Infect. Dis.* 2013; **57**: 267–74.
- Nam RK, Saskin R, Lee Y *et al.* Increasing hospital admission rates for urological complication after transrectal ultrasound guided prostate biopsy. *J. Urol.* 2013; **189**: S12–7.
- Roddam AW, Duffy MJ, Hamdy FC *et al.* Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2–10 ng/mL: systematic review and meta-analysis. *Eur. Urol.* 2005; **48**: 386–99.
- Vickers AJ, Savage C, O'Brien MF, Lilja H. Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *J. Clin. Oncol.* 2009; **27**: 398–403.
- Roobol MJ, Steyerberg EW, Kranse R *et al.* A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur. Urol.* 2010; **57**: 79–85.
- Di Silverio F, Gentile V, De Matteis A *et al.* Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. *Eur. Urol.* 2003; **43**: 164–75.
- Roehrborn CG, Kaplan SA, Noble WD *et al.* The impact of acute or chronic inflammation in baseline biopsy on the risk of clinical progression of BPH: results from the MTOPS study. *J. Urol.* 2005; **173**: 346.
- Nickel JC, Roehrborn CG, O'Leary MP, Bostwick DG, Somerville MC, Rittmaster RS. The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial. *Eur. Urol.* 2008; **54**: 1379–84.
- Shtricker A, Shefi S, Ringel A, Gillon G. PSA levels of 4.0 - 10 ng/mL and negative digital rectal examination. Antibiotic therapy versus immediate prostate biopsy. *Int. Braz. J. Urol.* 2009; **35**: 551–8.
- Heldwein FL, Teloken PE, Hartmann AA, Rhoden EL, Teloken C. Antibiotics and observation have a similar impact on asymptomatic patients with a raised PSA. *BJU Int.* 2011; **107**: 1576–81.
- Greiman A, Shah J, Bhavsar R *et al.* Six weeks of fluoroquinolone antibiotic therapy for patients with elevated serum prostate-specific antigen is not clinically beneficial: a randomized controlled clinical trial. *Urology* 2016; **90**: 32–7.
- Akduman B, Akduman D, Tokgöz H *et al.* Long-term fluoroquinolone use before the prostate biopsy may increase the risk of sepsis caused by resistant microorganisms. *Urology* 2011; **78**: 250–5.
- Ekici S, Cengiz M, Turan G, Alış EE. Fluoroquinolone-resistant acute prostatitis requiring hospitalization after transrectal prostate biopsy: effect of previous fluoroquinolone use as prophylaxis or long-term treatment. *Int. Urol. Nephrol.* 2012; **44**: 19–27.
- Kamijo T, Sato S, Kitamura T. Effect of cernitin pollen-extract on experimental nonbacterial prostatitis in rats. *Prostate* 2001; **49**: 122–31.
- Asakawa K, Nandachi N, Sato S *et al.* Effects of cernitin pollen-extract on inflammatory cytokines in sex-hormone-induced nonbacterial prostatitis rats. *Acta. Urol. Jpn.* 2001; **47**: 459–65.
- Carroll PR, Parsons JK, Andriole G *et al.* NCCN guidelines insights: prostate cancer early detection, version 2.2016. *J. Natl. Compr. Canc. Netw.* 2016; **14**: 509–19.
- Aslamazov EG, Akhvediani ND, Vinarov AZ, Aliaev IuG. Cernilton in the treatment of prostatic adenoma and chronic prostatitis. *Urologia.* 2007; **52**: 54–6.