Tumor volume and prostate-specific antigen kinetics effects on outcomes of metastatic prostate cancer patients receiving androgen deprivation therapy

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Abstract

Background The present study aimed to analyse the effects of androgen deprivation therapy (ADT) in patients with newly diagnosed metastatic castration-naïve prostate cancer (mCNPC) and explore predictors, particularly prostate-specific antigen (PSA) kinetics, associated with poor prognosis according to tumor volume, a new sub-classification of metastatic prostate cancer established by the CHAARTED trial.

Methods We reviewed 648 patients with newly diagnosed mCNPC receiving ADT at Chang Gung Memorial Hospital from January 2007 to December 2016. Basic characteristics and PSA kinetics profile were subsequently evaluated.

Results Among patients with high-volume disease, those with faster time to PSA nadir (TTN) (< 7 months), higher PSA nadir (≥ 2 ng/mL), and faster PSA doubling time (PSADT) (< 2 months) had higher risk for faster disease progression or shorter overall survival (OS) compared to those with slower TTN (> 7 months), lower PSA nadir (< 2 ng/mL), and slower PSADT (> 2 months). Multivariate analysis of those with low-volume disease showed that only PSADT (< 4 months) was tended to be associated with faster disease progression or shorter OS.

Conclusions PSA kinetics are effective clinical predictors for risk of disease progression and survival. Moreover, various PSA kinetics should be monitored according to tumor volume.

Background

Prostate cancer is one of the most common malignancies worldwide and the fourth most common cancer in Taiwan, with an age-standardised prostate cancer rate of 31.65 per 100,000 individuals in 2017 and metastatic prostate cancer (mPCa) accounting for nearly 30% of new cases.[1–4] Androgen deprivation therapy (ADT) has been the gold standard for patients with mPCa. Unfortunately, after receiving ADT, most of the prostate cancer cells develop drug resistance and progress to castration-resistant prostate cancer (CRPC), necessitating chemotherapy or another type of hormone therapy if feasible. Recent clinical trials and research have shown that upfront chemotherapy plus ADT promoted significantly longer overall survival (OS) in high-volume disease (HVD).[5–8] “Tumor volume”, a new sub-classification of metastatic prostate cancer established by the CHAARTED trial, can be classified as “high volume” (visceral metastases and/or four or more bone metastases with at least one outside the vertebral column and pelvis) or “low volume”. Moreover, this study showed that patients with HVD receiving a combination of ADT and chemotherapy had a longer median OS than those receiving ADT alone.[5]

Apart from tumor volume, prostate-specific antigen (PSA) has been recognised as an important biomarker for predicting treatment response and disease progression in prostate cancer during ADT. The PSA kinetics profile, including initial PSA level (iPSA),[9] time to PSA nadir (TTN),[9–12] nadir PSA level,[9, 13, 14] PSA decline pattern,[15–17] and PSA doubling time (PSADT),[18] had been shown to reflect tumor burden and predict outcomes in patients with prostate cancer under ADT. Other than PSA level and
related factors, pretreatment parameters, including Gleason grade group, haemoglobin (Hb), and alkaline phosphatase (ALP), have also been identified as prognostic or predictive biomarkers in patients with mPCa under ADT.[19]

Most previous studies had included populations comprising patients with metastatic castration-naïve prostate cancer (mCNPC) or metastatic castration-resistant prostate cancer (mCRPC). However, since the CHAARTED trial, the concept of tumor volume had been integrated into the management of metastatic prostate cancer. As such, identifying reliable early prognostic factors according to different tumor volumes during ADT would be helpful in the prompt formulation of better treatment strategies for patients with poor prognostic characteristics. While several studies have investigated factors influencing disease burden, such factors still remain unclear across different tumor volumes.[19, 20] Thus, the current study primarily aimed to explore the risk factors, particularly PSA kinetics, associated with poor prognosis, including shorter OS and shorter time to CRPC (the duration from initiation of ADT to biochemical CRPC status) according to tumor volume under ADT. Furthermore, we analysed the effects of ADT in patients with newly diagnosed mCNPC who had different tumor volumes.

**Methods**

We retrospectively evaluated patients with new metastatic prostate cancer diagnosed by histologic confirmation of at least one metastatic lesion after staging through computed tomography, magnetic resonance imaging, and/or bone scan according to the American Joint Committee on Cancer 8th edition between January 2007 to December 2016 who had received primary ADT (either surgical or medical castration, with or without anti-androgen) at Chang Gung Memorial Hospital (CGMH). Patients were grouped into HVD and low-volume disease (LVD) according to the CHAARTED trial, where HVD was defined as presence of visceral metastases and/or four or more bone metastases with at least one outside the vertebral column and pelvis. Patients who did not satisfy the aforementioned definition were classified as LVD. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Chang Gung Medical Foundation (IRB number 201801377B0), and patient consent is not required for observational studies.

CRPC was diagnosed based on biochemical progression (three consecutive spikes in PSA 1 week apart, of which two were 50% higher than the nadir, and PSA > 2 ng/mL) according to the European Association of Urology guideline. OS was defined as the period from diagnosis until death by any cause. Baseline patient demographics and post-treatment characteristics, including age at diagnosis, clinical M staging, iPSA (PSA level upon diagnosis), Gleason grade group (according to the classification of International Society of Urological Pathology[21]: Grade group 1, Gleason score ≤ 6; Grade group 2, Gleason score 3 + 4 = 7; Grade group 3, Gleason score 4 + 3 = 7; Grade group 4, Gleason score 8; and Grade group 5, Gleason score ≥ 9), initial Hb level, initial calcium (Ca) level and initial ALP level, were determined. PSA kinetics profiles were defined based on previous related studies,[11, 19, 22, 23] including TTN (defined as the duration from ADT initiation to PSA nadir), nadir PSA level, PSA reduction rate (PSARR) [defined as 100 × (iPSA - PSA nadir / iPSA) / TTN],[24] time to CRPC (the duration from ADT initiation to biochemical CRPC
status), time from PSA nadir to CRPC (TFNTC) (the duration from PSA nadir to CRPC status), and PSADT [defined as log2×(time interval)/log (PSA value) -log (nadir PSA)]. Patients with insufficient imaging reports for determining volume status or excessive missing data were excluded.

Previous studies have demonstrated that several cutoff points for PSA-related factors, including iPSA, TTN, PSA nadir, and PSADT, predicted disease progression or OS.[10, 11, 13, 24, 25] Moreover, some studies have utilised the receiver operating characteristic curve to determine cutoff points, while others use median values. The current study chose median values as the optimal cutoff points for the different parameters.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC). Nominal variables are presented as means and standard deviations, while non-nominal variables are presented as medians and interquartile ranges. The Chi-square test was used to compare categorical variables, while the independent t-test was used to compare continuous variables. OS and CPRC-free survival were evaluated using the Kaplan–Meier method. The multivariate Cox proportional-hazards model was used to determine the association between risk factors and OS or CPRC-free survival. All p values reported were two sided with p < 0.05 indicating statistical significance.

Results

A total of 918 patients with newly diagnosed metastatic prostate cancer at CGMH from January 2007 to December 2016 were identified. After excluding those who had received either chemotherapy or radiotherapy and those with incomplete information, a total of 648 patients receiving primary ADT were ultimately analysed. In the study population (Table 1), included patients had a median age of 75 (IQR 68–80) years, with 352 (54.3%) classified as HVD and 296 (45.7%) as LVD according to the CHAARTED trial. A total of 371 (57%) patients died during the study period. The median OS was 34 months (Table 2), while those with HVD had a significant shorter median OS than those with LVD (30 vs. 43 months; p < 0.0001) (Fig. 1a).

A total of 375 (57.9%) patients progressed to biochemical CRPC status (Table 2), among whom 232 (65.9%) had HVD and 143 (48.3%) had LVD. The median time to CRPC in all patients, those with HVD and those with LVD was 16.5, 13, and 26 months, respectively (p < 0.0001) (Fig. 1b). Significant differences in baseline characteristics and PSA kinetics, including Hb, ALP, iPSA, Gleason grade group, TTN, PSARR, PSA nadir level, TFNTC and PSADT, were observed between patients with HVD and LVD (Table 1).

Multivariate analysis of all included patients (mCNPC) revealed that those with TTN < 9 months, nadir PSA level ≥ 1 ng/mL, and PSADT < 3 months had increased tendency for biochemical progression (Table 3), while those with TTN < 9 months, nadir PSA level ≥ 1 ng/mL, duration of PSA nadir < 5 months, PSADT < 3 months, and time to CRPC < 17 months had increased risk for shorter OS (Table 4). Moreover, univariate and multivariate analyses of factors affecting disease progression to CRPC and OS in HVD and LVD are done. Accordingly, multivariate analysis of patients with HVD showed that those with faster TTN (< 7 months), higher PSA nadir (≥ 2 ng/mL), and faster PSADT (< 2 months) had higher risk for
faster disease progression or shorter OS compared to those with slower TTN (> 7 months), lower PSA nadir (< 2 ng/mL), and slower PSADT (> 2 months), respectively (Tables 5 and 6). Multivariate analysis of patients with LVD showed that only PSADT (< 4 months) was associated with increased risk for faster disease progression to CRPC or shorter OS (Tables 7 and 8).

**Discussion**

Research has shown that upfront chemotherapy with first-line ADT significantly improved OS in patients with high-volume metastatic hormone-sensitive prostate cancer.[5] Accordingly, previous studies had identified age, ECOG, Gleason grade group, pretreatment Hb, ALP, LDH, nadir PSA level, TTN and PSADT as prognostic factors for mPCa.[9, 19, 22] Apart from the aforementioned factors, Guangjie et al. demonstrated that patients who exhibited a rapid decrease in PSA levels during the initial ADT phase were at increased risk for progression to CRPC.[16] Masahiko Nakayama et al. introduced the concept that PSA kinetics and early PSA decline were associated differently with time to PSA progression in patients with mCRPC receiving abiraterone acetate. However, the aforementioned study had a limited number of patients and events.[26] Accordingly, the present study found that PSA kinetics was strongly associated with either risk for disease progression or OS. To date, three major clinical trials, namely GETUG-AFU 15, CHAARTED and STAMPEDE, had investigated the role of docetaxel in hormone-sensitive prostate cancer. All three studies had incorporated early chemohormonal therapy into their treatment stagey for mHSPC.[27] Among the overmentioned trials, only CHAARTED had classified the study groups based on tumor volume, subsequently demonstrating a statistically significant improvement in OS for patients with HVD on chemohormonal therapy.[27]

HVD accounted for 54% of our study population, 63% of that in the CHARTEED trial, and 49% of that in previous studies within Taiwan.[20] This indicates that Asian men had a lower prevalence of HVD than the occidental population, which corresponds with our general conception that prostate cancer incidence rates are higher among occidental than among Asian men.[28] The present study found that patients on ADT with HVD had significant shorter OS (30 vs. 43 months) and time to the development of CRPC (13 vs. 26 months) compared to those with LVD. This indicates that regardless of whether patients received chemohormonal therapy[29] or ADT alone, those with HVD had worse prognosis than those with LVD, which agrees with the general consensus that HVD promotes worse prognosis due to disease severity. The current study also found that 58% of the patients progressed to CRPC status, among whom 66% and 48% had HVD and LVD, respectively (p < 0.0001). The findings obtained herein were similar to those presented in previous studies, which demonstrated CRPC status in over 50%, and even 60–70%, of patients with mPCa[16, 20, 22, 30] and showed that over half of the patients with mPCa under ADT eventually progressed to CRPC. Furthermore, the present study found significant differences in PSA kinetics and factors affecting OS and disease progression to CRPC between HVD and LVD. Accordingly, TTN, nadir PSA, level and PSADT were identified as significant predictors of both OS and progression to CRPC in HVD, whereas only PSADT was identified as a significant predictor in LVD. The aforementioned results indicated that among patients with HVD, more attention should be provided to those with faster TTN, higher nadir PSA level and faster PSADT, with such patients possibly becoming suitable candidates
for upfront chemotherapy or new generation hormone therapy. However, among patients with LVD, more attention should be provided to those with increasing PSA levels and PSADT considering that TTN, PSA nadir and even PSA reduction rates were not major predictors.

PSA level has been the most widely used biomarker for evaluating disease progression and predicting survival in clinical practice. Furthermore, several retrospective clinical studies and even some meta-analyses have determined that PSA kinetics, including PSA response, nadir PSA level, TTN, or PSADT, predicted OS or disease progression.[9, 10, 13, 24] Among such factors, nadir PSA levels and TTN have been considered important predictors of survival and progression period. Generally, a faster decline in PSA levels has been associated with more cancer cell death, which promotes a more favourable prognosis and survival.[31] However, reports have shown that rapidly decreasing PSA levels during initial ADT was a risk factor for early progression to CRPC.[16] Accordingly, a recent study introduced the novel concept suggesting that tumor-regulating fibroblasts play an important role in the mechanisms associated with TTN after primary ADT.[32] Other studies have also demonstrated that rapidly decreasing PSA levels may be associated with transcriptional outcomes of ADT rather than cancer cell death. Moreover, heterogeneous prostate cancer cells, including hormone-resistant prostate cancer cells and hormone-sensitive prostate cancer cells, often coexist in the same patient. The rapid decline in PSA levels may indicate downregulation of PSA expression in hormone-sensitive prostate cancer cells, which are regulated by androgen via the androgen receptor pathway,[33] though it is doubtful that whether hormone-sensitive prostate cancer cells account for more of the cancer cells in HVD than in LVD, it might be a possible explanation for patient with HVD have shorter TTN and faster time to disease progression, even shorter OS. Moreover, longer TTN and lower PSA nadir levels during ADT have been known to be associated with significantly longer OS and period of disease progression.[10, 11, 13, 24, 30] Despite the lack of internationally accepted PSA nadir or TTN cutoff points for predicting disease progression or survival outcomes until present, observed tendencies have suggested that higher PSA nadir levels and shorter TTN promoted a shorter disease progression period and poor prognosis and survival of patients with mPCa receiving ADT.[9]

PSADT predicts outcomes has been known for nearly 30 years, and it may closely indicate changes in prostate tumor volume, an independent predictor of biochemical relapse among patients that either underwent radical prostatectomy or endocrine treatment.[34] Doctor D'Amico et al. demonstrated that patients with PSADT > 12 months have lower risk of prostate cancer death within 5 years of relapse.[35] Moreover, Kelloff et al. reported that PSADT was a predictor of tumor response to medication in patients with prostate cancer and suggested that significant changes in PSADT may be used to support the approval of newer treatment.[36] Despite the considerably wide distribution of PSADT values, studies have suggested that it may still be useful for strategies after relapse and that patients with advanced or relapsed disease who have rapid PSADT should receive more aggressive or earlier treatment.[37, 38] Tomioka,S. et al. also reported that post-treatment PSADT ≤ 2 months may be a predictor for decreased survival and was associated with poor prognosis among patients with prostate cancer and bone metastasis.[39] The present study identified lower cutoff point of PSADT than before as a useful clinical predictor in patients with mPCa receiving ADT, regardless of whether they had HVD (PSADT < 2 months)
or LVD (PSADT < 4 months). The possible cause of short median PSADT in our study is that the PSA nadir level is low, so that the doubled PSA level could be reached easily. In addition, PSA level is checked more frequently in our study than in other studies, so the PSADT may also be influenced. Although PSADT cannot be evaluated during the early stages of ADT, it may still be a clinically effective predictor of disease progression and OS.

Previous reports have showed that PSA-producing CRPC cells have the ability to grow under low androgen environments and may be present in heterogeneous prostate cancer with bone metastases.[29, 40] Moreover, CRPC cells may exhibit faster PSA decline under ADT compared to androgen-dependent prostate cancer cells due to the rapid reduction in PSA, which may be affected via the downregulation of PSA expression, regulated by androgen through androgen receptors, rather than cancer cell death. Another explanation is that the rapid removal of androgen-dependent prostate cancer cells may provide a suitable environment for CRPC cells.[29, 33] Given that HVD has been associated with a higher CRPC rate and more severe bone metastases and disease status compared to LVD, TTN and PSA nadir might be more effective predictors for OS and disease progression in HVD rather than in LVD.

The current study has some limitations worth noting. The most important limitation is our exclusion of patients who received chemotherapy or radiotherapy, however those with subsequent hormone therapy, including abiraterone or enzalutamide after CRPC were not excluded, which may have affected our results with regard to OS. Second, given that this was a single-centre retrospective study, our results may not be generalisable to other populations. Moreover, considering that CGMH is a medical centre in Taiwan, the disease severities of our study population may be higher than those of general population. Lastly, not all PSA parameters and factors, including Gleason score, Hb, Ca and ALP, were regularly assessed at our institution, which might have influenced our results.

**Conclusion**

Among patients receiving ADT, those with high-volume metastatic prostate cancer had significantly shorter OS and faster disease progression compared to those with low-volume metastatic prostate cancer. Moreover, the current study identified TTN ≥ 7 months, nadir PSA level ≤ 2 ng/mL, and PSADT ≥ 2 months as significant predictors of slower disease progression and better OS in HVD. However, only PSADT ≥ 4 months had been identified as an effective predictor for slower disease progression and better OS in LVD. PSA kinetics can therefore be effective clinical predictors of disease progression and survival. Furthermore, different PSA kinetics should be carefully monitored according to different tumor volumes. Patients under ADT with shorter TTN and faster PSADT might be suitable for further treatment earlier.

**Abbreviations**

mPCa
metastatic prostate cancer
ADT
Androgen deprivation therapy

CRPC
castration-resistant prostate cancer

OS
overall survival

HVD
high-volume disease

PSA
prostate-specific antigen

iPSA
initial PSA level

TTN
time to PSA nadir

PSADT
PSA doubling time

Hb
haemoglobin

ALP
alkaline phosphatase

mCNPC
metastatic castration-naïve prostate cancer

mCRPC
metastatic castration-resistant prostate cancer

LVD
low-volume disease

Ca
calcium

PSARR
PSA reduction rate

TFNDC
time from PSA nadir to CRPC

Declarations

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Ethics declarations

Ethics approval and consent to participate

Patient consent is not required for observational studies, and this study was approved by the Institutional Review Board (IRB) of Chang Gung Medical Foundation (IRB number 201801377B0).

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Conflict of interest

The authors declare no competing interests.

Data availability

This study is based in part on data from the Chang Gung Research Database provided by Chang Gung Memorial Hospital. The interpretation and conclusions contained herein do not represent the position of Chang Gung Memorial Hospital.
Contributions

Y.C. Lin: study design, data collection, quality control of data, data analysis, statistical analysis, data interpretation, authored the manuscript. J.L. Huang: data collection, quality control of data, data analysis, statistical analysis.

P.H. Lin, I.H. Shao, and Y.C. Chu: study design and manuscript review. H.C. Kan, C.Y. Liu, K.J. Yu, Y.H. Chang and S.T. Pang: study design. C.K. Chuang: study design, quality control of data, manuscript editing and manuscript review

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Consent for publication

Not applicable.

References

1. Grossman DC, Curry SJ, Owens DK, Bibbins-Domingo K, Caughey AB, Davidson KW, et al. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. Jama 2018;319(18):1901–13.

2. Hung C-F, Yang C-K, Ou Y-C. Urologic cancer in Taiwan. Japanese journal of clinical oncology 2016;46(7):605–9.

3. Health Promotion Administration MoHaW. Cancer registry annual report, 2017, Taiwan. Taiwan: Health Promotion Administration, Ministry of Health and Welfare; 2019:3.

4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer 2015;136(5):E359-E86.

5. Sweeney CJ, Chen Y-H, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. New England Journal of Medicine 2015;373(8):737–46.

6. Kwon W-A, Joung JY, Lee JE, Choi SY, Kim SH, Seo HK, et al. Use of docetaxel plus androgen deprivation therapy for metastatic hormone-sensitive prostate cancer in Korean patients: A retrospective study. Investigative and clinical urology 2019;60(3):195–201.

7. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE):
survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. The Lancet 2016;387(10024):1163–77.

8. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. The lancet oncology 2013;14(2):149–58.

9. Afriansyah A, Hamid ARAH, Mochtar CA, Umbas R. Prostate specific antigen (PSA) kinetic as a prognostic factor in metastatic prostate cancer receiving androgen deprivation therapy: systematic review and meta-analysis. F1000Research 2018;7.

10. Teoh JYC, Tsu JHL, Yuen SKK, Chan SYS, Chiu PKF, Lee W-M, et al. Prognostic significance of time to prostate-specific antigen (PSA) nadir and its relationship to survival beyond time to PSA nadir for prostate cancer patients with bone metastases after primary androgen deprivation therapy. Annals of surgical oncology 2015;22(4):1385–91.

11. Huang SP, Bao BY, Wu MT, Choueiri TK, Goggins WB, Huang CY, et al. Impact of prostate-specific antigen (PSA) nadir and time to PSA nadir on disease progression in prostate cancer treated with androgen-deprivation therapy. The Prostate 2011;71(11):1189–97.

12. Choueiri TK, Xie W, D'amico AV, Ross RW, Hu JC, Pomerantz M, et al. Time to prostate-specific antigen nadir independently predicts overall survival in patients who have metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy. Cancer: Interdisciplinary International Journal of the American Cancer Society 2009;115(5):981–7.

13. Tomioka A, Tanaka N, Yoshikawa M, Miyake M, Anai S, Chihara Y, et al. Nadir PSA level and time to nadir PSA are prognostic factors in patients with metastatic prostate cancer. BMC urology 2014;14(1):33.

14. Zietman A, Tibbs M, Dallow K, Smith C, Althausen A, Zlotecki R, et al. Use of PSA nadir to predict subsequent biochemical outcome following external beam radiation therapy for T1-2 adenocarcinoma of the prostate. Radiotherapy and oncology 1996;40(2):159–62.

15. Akbay E, Bozlu M, Çayan S, Kara PÖ, Tek M, Aytekin C. Prostate-specific antigen decline pattern in advanced prostate cancer receiving androgen deprivation therapy and relationship with prostate-specific antigen progression. The Aging Male 2017;20(3):175–83.

16. Ji G, Song G, Huang C, He S, Zhou L. Rapidly decreasing level of prostate-specific antigen during initial androgen deprivation therapy is a risk factor for early progression to castration-resistant prostate cancer: A retrospective study. Medicine 2017;96(36).

17. Koo KC, Park SU, Kim KH, Rha KH, Hong SJ, Yang SC, et al. Predictors of survival in prostate cancer patients with bone metastasis and extremely high prostate-specific antigen levels. Prostate international 2015;3(1):10–5.

18. Semeniuk RC, Venner PM, North S. Prostate-specific antigen doubling time is associated with survival in men with hormone-refractory prostate cancer. Urology 2006;68(3):565–9.

19. Terada N, Akamatsu S, Kobayashi T, Inoue T, Ogawa O, Antonarakis ES. Prognostic and predictive biomarkers in prostate cancer: latest evidence and clinical implications. Therapeutic advances in
medical oncology 2017;9(8):565–73.

20. Cheng Y-T, Hong J-H, Lu Y-C, Pu Y-S, Huang C-Y, Huang K-H, et al. Impact of high-volume disease in Asian population with newly diagnosed metastatic prostate cancer. Urological Science 2018;29(3):136.

21. Delahunt B, Egevad L, Srigley JR, Steigler A, Murray JD, Atkinson C, et al. Validation of International Society of Urological Pathology (ISUP) grading for prostatic adenocarcinoma in thin core biopsies using TROG 03.04 'RADAR'trial clinical data. Pathology 2015;47(6):520–5.

22. Lin T-T, Chen Y-H, Wu Y-P, Chen S-Z, Li X-D, Lin Y-Z, et al. Risk factors for progression to castration-resistant prostate cancer in metastatic prostate cancer patients. Journal of Cancer 2019;10(22):5608.

23. Tamada S, Iguchi T, Kato M, Asakawa J, Kita K, Yasuda S, et al. Time to progression to castration-resistant prostate cancer after commencing combined androgen blockade for advanced hormone-sensitive prostate cancer. Oncotarget 2018;9(97):36966.

24. Hamano I, Hatakeyama S, Narita S, Takahashi M, Sakurai T, Kawamura S, et al. Impact of nadir PSA level and time to nadir during initial androgen deprivation therapy on prognosis in patients with metastatic castration-resistant prostate cancer. World journal of urology 2019;37(11):2365–73.

25. Whitney CA, Howard LE, Freedland SJ, DeHoedt AM, Amling CL, Aronson WJ, et al. Impact of age, comorbidity, and PSA doubling time on long-term competing risks for mortality among men with non-metastatic castration-resistant prostate cancer. Prostate cancer and prostatic diseases 2019;22(2):252.

26. Nakayama M, Kobayashi H, Takahara T, Oyama R, Imanaka K, Yoshizawa K. Association of early PSA decline and time to PSA progression in abiraterone acetate-treated metastatic castration-resistant prostate cancer; a post-hoc analysis of Japanese phase 2 trials. BMC urology 2016;16(1):27.

27. Damodaran S, Kyriakopoulos CE, Jarrard DF. Newly diagnosed metastatic prostate cancer: has the paradigm changed? Urologic Clinics 2017;44(4):611–21.

28. Taitt HE. Global trends and prostate cancer: a review of incidence, detection, and mortality as influenced by race, ethnicity, and geographic location. American journal of men's health 2018;12(6):1807–23.

29. Yeung F, Li X, Ellett J, Trapman J, Kao C, Chung LW. Regions of prostate-specific antigen (PSA) promoter confer androgen-independent expression of PSA in prostate cancer cells. Journal of Biological Chemistry 2000;275(52):40846–55.

30. Sasaki T, Onishi T, Hoshina A. Cutoff value of time to prostate-specific antigen nadir is inversely correlated with disease progression in advanced prostate cancer. Endocrine Related Cancer 2012;19(5):725.

31. Arai Y, Yoshiki T, Yoshida O. Prognostic significance of prostate specific antigen in endocrine treatment for prostatic cancer. The Journal of urology 1990;144(6):1415–9.
32. Sasaki T, Sugimura Y. The importance of time to prostate-specific antigen (PSA) nadir after primary androgen deprivation therapy in hormone-naïve prostate cancer patients. Journal of clinical medicine 2018;7(12):565.

33. Sasaki T, Onishi T, Hoshina A. Nadir PSA level and time to PSA nadir following primary androgen deprivation therapy are the early survival predictors for prostate cancer patients with bone metastasis. Prostate cancer and prostatic diseases 2011;14(3):248–52.

34. Tisman G. Describing prostate Cancer dynamics: second look at PSA-doubling time and PSA-specific growth rate. Advances in Prostate Cancer 2013:177.

35. D'Amico AV, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. Journal of Clinical Oncology 2002;20(23):4567–73.

36. Kelloff GJ, Coffey DS, Chabner BA, Dicker AP, Guyton KZ, Nisen PD, et al. Prostate-specific antigen doubling time as a surrogate marker for evaluation of oncologic drugs to treat prostate cancer. Clinical cancer research 2004;10(11):3927–33.

37. Vickers AJ, Brewster SF. PSA velocity and doubling time in diagnosis and prognosis of prostate cancer. British Journal of Medical and Surgical Urology 2012;5(4):162–8.

38. Nakata S, Takahashi H, Takezawa Y, Kobayashi M, Matumoto K, Kosaku N, et al. PSA doubling time in prostate cancer relapsed after endocrine therapy. Nihon Hinyokika Gakkai zasshi The japanese journal of urology 2000;91(7–8):584–8.

39. Tomioka S, Shimbo M, Amiya Y, Nakatsu H, Murakami S, Shimazaki J. Significance of prostate-specific antigen-doubling time on survival of patients with hormone refractory prostate cancer and bone metastasis: Analysis on 56 cases of cancer-specific death. International journal of urology 2007;14(2):123–7.

40. Onishi T, Yamakawa K, Franco OE, Kawamura J, Watanabe M, Shiraishi T, et al. Mitogen-activated protein kinase pathway is involved in α6 integrin gene expression in androgen-independent prostate cancer cells: role of proximal Sp1 consensus sequence. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research 2001;1538(2–3):218–27.

Tables
Table 1. baseline characteristics

| Patient demographics | HVD(n=352, 54.3%) | LVD(n=296, 45.7%) | P value |
|----------------------|-------------------|-------------------|---------|
| Age, median, year (IQR) | 75(68-80)         | 74 (68-80)        | 0.2242  |
| M stage, n (%)        |                   | <0.0001           |
| 1A                   | 0                 | 72 (24.3%)        |
| 1B                   | 268 (76.1%)       | 224 (75.7%)       |
| 1C                   | 84 (23.9%)        | 0                 |
| Gleason grade group, n (%) |                | 0.0013            |
| 1                    | 0                 | 8 (3.3%)          |
| 2                    | 6 (2.1%)          | 12 (4.9%)         |
| 3                    | 26 (9.1%)         | 34 (13.9%)        |
| 4                    | 64 (22.3%)        | 47 (19%)          |
| 5                    | 191 (66.5%)       | 145 (58.9%)       |
| Initial PSA level, ng/ml, median (IQR) | 511.5 (181.25-1234.47) | 98.2 (45-256.6) | <0.0001 |
| Hb, g/dL, median (IQR) | 11.5 (9.7-13.2)  | 12.7 (11.6-13.9)  | <0.0001 |
| Ca, g/dL, median (IQR) | 8.7 (8.2-9.1)    | 8.8 (8.3-9.1)     | 0.9528  |
| ALP, U/L, median (IQR) | 146 (94-324)     | 74 (60-101)       | <0.0001 |
| CRPC, n(%)            |                   | <0.0001           |
| Yes                  | 232 (65.9%)       | 143 (48.3%)       |
| No                   | 120 (34.1%)       | 153 (51.7%)       |
| PSA kinetics after ADT|                  |                   |
| TTN, month, median (IQR) | 7.15 (3.7-13.3)  | 11.9 (6.25-20.9)  | <0.0001 |
| nadir PSA level, ng/ml, median (IQR) | 2.2 (0.23-17.18) | 0.23 (0.02-1.7)  | 0.0015  |
| PSA RR,%/month, median (IQR) | 12.5 (6.8-22.04) | 7.99 (4.38-14.9) | 0.0002  |
| TFNTE, month, median (IQR) | 3.25 (2.5-7.9)  | 8.3 (2.7-26.1)    | <0.0001 |
| PSADT, month, median (IQR) | 2.3 (1.4-4.15)  | 3.6 (1.9-7)       | <0.0001 |

CRPC: castration-resistant prostate cancer
TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTE: time from PSA nadir to CRPC,
PSADT: PSA doubling time
Table 2. Overall baseline characteristics
### Patient demographics

| Description                                      | All patients (n=648) |
|--------------------------------------------------|----------------------|
| Age, median, year (IQR)                          | 75 (68-80)           |
| Overall survival, median, month (IQR)            | 34 (21-58)           |
| Time to CRPC, median, month (IQR)                | 16.5 (8-36)          |
| M stage, n (%)                                   |                      |
| 1A                                               | 72 (11.11%)          |
| 1B                                               | 492 (75.93%)         |
| 1C                                               | 84 (12.96%)          |
| Gleason grade group, n (%)                       |                      |
| 1                                                | 8 (1.5%)             |
| 2                                                | 18 (3.38%)           |
| 3                                                | 60 (11.26%)          |
| 4                                                | 111 (20.83%)         |
| 5                                                | 336 (63.04%)         |
| missing                                          | 115                  |
| Initial PSA level, ng/ml, median (IQR)           | 243.9 (74.9-790.8)   |
| Hb, g/dL, median (IQR)                           | 12.1 (10.3-13.5)     |
| Ca, g/dL, median (IQR)                           | 8.7 (8.3-9.1)        |
| ALP, U/L, median (IQR)                           | 118 (75-227)         |
| CRPC, n (%)                                      |                      |
| Yes                                              | 375 (57.9%)          |
| No                                               | 273 (42.1%)          |

| Description                                      | All patients (n=648) |
|--------------------------------------------------|----------------------|
| PSA kinetics after ADT                           |                      |
| TTN, month, median (IQR)                         | 8.7 (4.8-16.65)      |
| nadir PSA level, ng/ml, median (IQR)             | 0.86 (0.07-5.99)     |
| PSA RR, %/month, median (IQR)                    | 10.32 (5.62-18.17)   |
| TFNTC, month, median (IQR)                       | 4.5 (2.7-15.1)       |
| PSADT, month, median (IQR)                       | 2.6 (1.5-5.3)        |

CRPC: castration-resistant prostate cancer
TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTC: time from PSA nadir to CRPC, PSADT: PSA doubling time
| Factors                      | Univariate | Multivariate |
|-----------------------------|------------|--------------|
|                             | Hazard ratio(95% CI) | P value | Hazard ratio(95% CI) | P value |
| **Age**                     |            |              |                      |         |
| <75                         | 1(reference) |          |                      |         |
| >=75                        | 0.97 (0.79-1.18) | 0.731 | --                   |         |
| **Gleason grade group**     |            |              |                      |         |
| <4                          | 1(reference) |          |                      |         |
| >=4                         | 1.75 (1.25-2.46) | 0.001 | --                   |         |
| **Initial PSA level, ng/ml**|            |              |                      |         |
| <250                        | 1(reference) |          |                      |         |
| >=250                       | 1.69 (1.34-2.14) | <0.0001 | --                   |         |
| **TTN, month**              |            |              |                      |         |
| <9                          | 1(reference) |          |                      |         |
| >=9                         | 0.27 (0.22-0.33) | <0.0001 | 0.22 (0.11-0.44) | <0.0001 |
| **Nadir PSA level, ng/ml**  |            |              |                      |         |
| <1                          | 1(reference) |          |                      |         |
| >=1                         | 3.78 (2.93-4.88) | <0.0001 |                      |         |
| **PSARR, %/month**          |            |              |                      |         |
| <10                         | 1(reference) |          |                      |         |
| >=10                        | 3.76 (2.93-4.81) | <0.0001 |                      |         |
| **TFNTC, month**            |            |              |                      |         |
| <5                          | 1(reference) |          |                      |         |
| >=5                         | 0.19 (0.15-0.24) | <0.0001 | 1.37 (0.99-1.89) | 0.059   |
| **PSADT, month**            |            |              |                      |         |
| <3                          | 1(reference) |          |                      |         |
| >=3                         | 0.34 (0.26-0.44) | <0.0001 | 0.34 (0.25-0.48) | <0.0001 |

TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTC: time from PSA nadir to CRPC, PSADT: PSA doubling time
| Factors                     | Univariate                      |                  | Multivariate       |                  |
|-----------------------------|---------------------------------|------------------|--------------------|------------------|
|                             | Hazard ratio (95% CI)           | P value          | Hazard ratio (95% CI) | P value          |
| Age                         |                                 |                  |                    |                  |
| <75                         | 1 (reference)                   |                  |                    |                  |
| >=75                        | 1.37 (0.11-1.68)                | <0.001           | --                 |                  |
| Gleason grade group         |                                 |                  |                    |                  |
| <4                          | 1 (reference)                   |                  |                    |                  |
| >=4                         | 1.82 (1.29-2.59)                | <0.0001          | --                 |                  |
| Initial PSA level, ng/ml    |                                 |                  |                    |                  |
| <250                        | 1 (reference)                   |                  |                    |                  |
| >=250                       | 1.29 (1.03-1.62)                | 0.030            | --                 |                  |
| TTN, month                  |                                 |                  |                    |                  |
| <9                          | 1 (reference)                   |                  |                    | 1 (reference)    |
| >=9                         | 0.25 (0.20-0.31)                | <0.0001          | 0.24 (0.12-0.48)   | <0.0001          |
| Nadir PSA level, ng/ml      |                                 |                  |                    |                  |
| <1                          | 1 (reference)                   |                  |                    | 1 (reference)    |
| >=1                         | 3.66 (2.86-4.68)                | <0.0001          | 2.76 (1.98-3.84)   | <0.0001          |
| PSARR, %/month              |                                 |                  |                    |                  |
| <10                         | 1 (reference)                   |                  |                    | 1 (reference)    |
| >=10                        | 3.51 (2.73-4.51)                | <0.0001          | 0.53 (0.27-1.04)   | 0.065            |
| TFNTC, month                |                                 |                  |                    |                  |
| <5                          | 1 (reference)                   |                  |                    | 1 (reference)    |
| >=5                         | 0.38 (0.30-0.47)                | <0.0001          | 1.67 (1.18-2.37)   | 0.004            |
| PSADT, month                |                                 |                  |                    |                  |
| <3                          | 1 (reference)                   |                  |                    | 1 (reference)    |
| >=3                         | 0.25 (0.19-0.34)                | <0.0001          | 0.40 (0.28-0.56)   | <0.0001          |
| TTC, month                  |                                 |                  |                    |                  |
| <17                         | 1 (reference)                   |                  |                    | 1 (reference)    |
| \( \geq 17 \) | 0.20 (0.16-0.25) | <0.0001 | 0.53 (0.32-0.85) | 0.009 |

TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTC: time from PSA nadir to CRPC, PSADT: PSA doubling time, TTC: Time from ADT to CRPC
| Factors                        | Univariate |            | Multivariate |            |
|-------------------------------|------------|------------|--------------|------------|
|                              | Hazard ratio(95% CI) | P value | Hazard ratio(95% CI) | P value |
| Age                           |            |           |              |           |
| <75                           | 1(reference) |          |              |           |
| >=75                          | 0.93(0.72-1.21) | 0.605    |              |           |
|                              |            |           |              |           |
| Gleason grade group           |            |           |              |           |
| <4                            | 1(reference) |          |              |           |
| >=4                           | 1.23(0.76-1.97) | 0.398    |              |           |
|                              |            |           |              |           |
| Initial PSA level, ng/ml      |            |           |              |           |
| <500                          | 1(reference) |          |              |           |
| >=500                         | 1.39(1.04-1.87) | 0.026    |              |           |
|                              |            |           |              |           |
| TTN, month                    |            |           |              |           |
| <7                            | 1(reference) |          | 1(reference) |           |
| >=7                           | 0.34(0.26-0.44) | <0.0001 | 0.19(0.09-0.38) | <0.0001 |
|                              |            |           |              |           |
| Nadir PSA level, ng/ml        |            |           |              |           |
| <2                            | 1(reference) |          | 1(reference) |           |
| >=2                           | 2.04(1.51-2.76) | <0.0001 | 2.44(1.71-3.50) | <0.0001 |
|                              |            |           |              |           |
| PSARR, %/month                |            |           |              |           |
| <13                           | 1(reference) |          | 1(reference) |           |
| >=13                          | 2.89(2.14-3.90) | <0.0001 | 0.72(0.37-1.38) | 0.318    |
|                              |            |           |              |           |
| TFNTE, month                  |            |           |              |           |
| <3                            | 1(reference) |          | 1(reference) |           |
| >=3                           | 0.26(0.20-0.34) | <0.0001 | 1.15(0.81-1.64) | 0.429    |
|                              |            |           |              |           |
| PSADT, month                  |            |           |              |           |
| <2                            | 1(reference) |          | 1(reference) |           |
| >=2                           | 0.46(0.33-0.63) | <0.0001 | 0.51(0.35-0.75) | 0.001    |

TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTE: time from PSA nadir to CRPC, PSADT: PSA doubling time
| Factors                        | Univariate |                  | P value | Multivariate |                  | P value |
|-------------------------------|------------|------------------|---------|--------------|------------------|---------|
|                               | hazard ratio(95% CI) |                  |         | hazard ratio(95% CI) |                  |         |
| Age                           |            |                  |         |              |                  |         |
| <75                           | 1 (reference) |                  |         |              |                  |         |
| >=75                          | 0.94 (0.67-1.30) | 0.699            |         |              |                  |         |
| Gleason grade group           |            |                  |         |              |                  |         |
| <4                            | 1 (reference) |                  |         |              |                  |         |
| >=4                           | 1.82 (1.13-2.96) | 0.015            |         |              |                  |         |
| Initial PSA level, ng/ml      |            |                  |         |              |                  |         |
| <100                          | 1 (reference) |                  |         |              |                  |         |
| >=100                         | 1.03 (0.71-1.51) | 0.864            |         |              |                  |         |
| TTN, month                    |            |                  |         |              |                  |         |
| <12                           | 1 (reference) |                  |         |              |                  |         |
| >=12                          | 0.25 (0.18-0.36) | <0.0001          |         | 0.31 (0.05-2.01) | 0.222 |
| Nadir PSA level, ng/ml        |            |                  |         |              |                  |         |
| <0.2                          | 1 (reference) |                  |         |              |                  |         |
| >=0.2                         | 5.61 (3.62-8.69) | <0.0001          |         | 2.09 (0.88-4.94) | 0.094 |
| PSARR, %/month                |            |                  |         |              |                  |         |
| <8                            | 1 (reference) |                  |         |              |                  |         |
| >=8                           | 4.20 (2.79-6.35) | <0.0001          |         | 0.79 (0.13-4.86) | 0.802 |
| TFNTC, month                  |            |                  |         |              |                  |         |
| <8                            | 1 (reference) |                  |         |              |                  |         |
| >=8                           | 0.18 (0.12-0.26) | <0.0001          |         | 0.97 (0.38-2.46) | 0.944 |
| PSADT, month                  |            |                  |         |              |                  |         |
| <4                            | 1 (reference) |                  |         |              |                  |         |
| >=4                           | 0.45 (0.30-0.68) | <0.0001          |         | 0.31 (0.16-0.61) | 0.001 |

TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTC: time from PSA nadir to CRPC, PSADT: PSA doubling time
| Factors                      | Univariate |               | Multivariate |               |
|------------------------------|------------|---------------|--------------|---------------|
|                              | Hazard ratio(95% CI) | P value | Hazard ratio(95% CI) | P value |
| Age                          |            |               |              |              |
| <75                          | 1(reference) |       |              |              |
| >=75                         | 1.23 (0.95-1.59) | 0.115 |              |              |
| Gleason grade group           |            |               |              |              |
| <4                           | 1(reference) |       |              |              |
| >=4                          | 1.44 (0.87-2.37) | 0.152 |              |              |
| Initial PSA level, ng/ml     |            |               |              |              |
| <500                         | 1(reference) |       |              |              |
| >=500                        | 0.96 (0.72-1.27) | 0.781 |              |              |
| TTN, month                   |            |               |              |              |
| <7                           | 1(reference) |       |              |              |
| >=7                          | 0.21 (0.16-0.28) | <0.0001 | 0.19 (0.09-0.38) | <0.0001 |
| Nadir PSA level, ng/ml       |            |               |              |              |
| <2                           | 1(reference) |       |              |              |
| >=2                          | 3.35 (2.47-4.54) | <0.0001 | 2.32 (1.61-3.34) | <0.0001 |
| PSARR, %/month               |            |               |              |              |
| <13                          | 1(reference) |       |              |              |
| >=13                         | 2.78 (2.06-3.75) | <0.0001 | 0.59 (0.30-1.15) | 0.121 |
| TFNTE, month                 |            |               |              |              |
| <3                           | 1(reference) |       |              |              |
| >=3                          | 0.34 (0.24-0.48) | <0.0001 | 1.28 (0.89-1.85) | 0.185 |
| PSADT, month                 |            |               |              |              |
| <2                           | 1(reference) |       |              |              |
| >=2                          | 0.26 (0.20-0.34) | <0.0001 | 0.53 (0.36-0.78) | 0.001 |
| TTC, month                   |            |               |              |              |
| <13                          | 1(reference) |       |              |              |
| >=13 | 0.26(0.20-0.34) | <0.0001 | 0.63(0.39-1.00) | 0.051 |

TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTC: time from PSA nadir to CRPC,
PSADT: PSA doubling time, TTC: Time from ADT to CRPC
| Factors                      | Univariate                     | Multivariate                   |
|-----------------------------|--------------------------------|--------------------------------|
|                             | Hazard ratio (95% CI)          | P value                        | Hazard ratio (95% CI) | P value |
| Age                         |                                |                                |                      |        |
| <75                         | 1 (reference)                  |                                |                      |        |
| >=75                        | 1.64 (1.15-2.32)               | 0.006                          |                      |        |
| Gleason grade group         |                                |                                |                      |        |
| <4                          | 1 (reference)                  |                                |                      |        |
| >=4                         | 1.71 (1.04-2.82)               | 0.034                          |                      |        |
| Initial PSA level, ng/ml    |                                |                                |                      |        |
| <100                        | 1 (reference)                  |                                |                      |        |
| >=100                       | 1.00068-1.48                   | 0.995                          |                      |        |
| TTN, month                  |                                |                                |                      |        |
| <12                         | 1 (reference)                  |                                |                      |        |
| >=12                        | 0.30 (0.21-0.44)               | <0.0001                        | 0.32 (0.05-1.93)     | 0.214   |
| Nadir PSA level, ng/ml      |                                |                                |                      |        |
| <0.2                        | 1 (reference)                  |                                |                      |        |
| >=0.2                       | 3.37 (2.20-5.17)               | <0.0001                        | 1.87 (0.78-4.49)     | 0.159   |
| PSARR, %/month              |                                |                                |                      |        |
| <8                          | 1 (reference)                  |                                |                      |        |
| >=8                         | 3.99 (2.58-6.19)               | <0.0001                        | 0.71 (0.12-4.13)     | 0.703   |
| TFNTC, month                |                                |                                |                      |        |
| <8                          | 1 (reference)                  |                                |                      |        |
| >=8                         | 0.28 (0.19-0.40)               | <0.0001                        | 1.21 (0.46-3.19)     | 0.706   |
| PSADT, month                |                                |                                |                      |        |
| <4                          | 1 (reference)                  |                                |                      |        |
| >=4                         | 0.19 (0.11-0.32)               | <0.0001                        | 0.35 (0.17-0.71)     | 0.004   |
| TTC, month                  |                                |                                |                      |        |
| <26                         | 1 (reference)                  |                                |                      |        |
| >=26 | 0.18(0.12-0.26) | <0.0001 | 0.57(0.20-1.64) | 0.298 |

TTN: Time to PSA nadir, PSARR: PSA reduction rate, TFNTC: time from PSA nadir to CRPC, PSADT: PSA doubling time, TTC: Time from ADT to CRPC