Clinical association between pre-treatment levels of plasma fibrinogen and bone metastatic burden in newly diagnosed prostate cancer patients

Gan-Sheng Xie, Gang Li, Yu Li, Jin-Xian Pu, Yu-Hua Huang, Jin-Hu Li, Hu-Ming Yin

Department of Urology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215031, China.

Abstract

Background: Due to the different treatments for low-volume metastatic prostate cancer (PCa) as well as high-volume ones, evaluation of bone metastatic status is clinically significant. In this study, we evaluated the correlation between pre-treatment plasma fibrinogen and the burden of bone metastasis in newly diagnosed PCa patients.

Methods: A single-center retrospective analysis, focusing on prostate biopsies of newly diagnosed PCa patients, was performed. A total of 261 patients were enrolled in this study in a 4-year period. All subjects were submitted to single-photon emission computerized tomography-computed tomography to confirm the status of bone metastasis and, if present, the number of metastatic lesions would then be calculated. Clinical information such as age, prostate-specific antigen (PSA), fibrinogen, clinical T stage, and Gleason score were collected. Patients were divided into three groups: (i) a non-metastatic group, (ii) a high volume disease (HVD) group (>3 metastases with at least one lesion outside the spine), and (iii) a low volume disease (LVD) group (metastatic patients excluding HVD ones). The main statistical methods included non-parametric Mann-Whitney test, Spearman correlation, receiver operating characteristic (ROC) curves, and logistic regression.

Results: Fibrinogen positively correlated with Gleason score ($r = 0.180$, $P = 0.003$), PSA levels ($r = 0.216$, $P < 0.001$), and number of metastatic lesions ($r = 0.296$, $P < 0.001$). Compared with the non-metastatic and LVD groups, the HVD group showed the highest PSA (104.98 ng/mL, median) and fibrinogen levels (3.39 g/L, median), as well as the largest proportion of Gleason score >7 (86.8%). Both univariate (odds ratio [OR] = 2.16, 95% confidential interval [CI]: 1.536–3.038, $P < 0.001$) and multivariate (OR = 1.726, 95% CI: 1.206–2.472, $P = 0.003$) logistic regressions showed that fibrinogen was independently associated with HVD. The ROC curve suggested that fibrinogen acts as a predictor of HVD patients, yielding a cut-off of 3.08 g/L, with a sensitivity of 0.684 and a specificity of 0.760 (area under the curve = 0.739, 95% CI: 0.644–0.833, $P < 0.001$).

Conclusions: Pre-treatment plasma fibrinogen is positively associated with bone metastatic burden in PCa patients. Our results indicate that fibrinogen might be a potential predictor of HVD.

Keywords: Prostate cancer; Fibrinogen; Prostate-specific antigen; Metastasis; Biopsy

Introduction

A number of studies have indicated an association between cancer and hemostasis, with the detection of high levels of coagulation markers in cancer patients.[1] Fibrinogen is a 340,000 Da glycoprotein that is mainly synthesized in hepatocytes. It intensively participates in the coagulation cascade, where it can be converted to insoluble fibrin by activated thrombin.[2] Typically, plasma fibrinogen levels increase in certain malignant states and systemic inflammation. Fibrinogen has also been considered an unfavorable prognostic factor in some malignancies, such as cancers of digestive system, gynecologic and urologic neoplasms, and soft tissue sarcomas.[3] A significant association between fibrinogen levels and prostate carcinogenesis has also been reported.[4] Interestingly, prostate cancer (PCa) patients with hyperfibrinogenemia are more likely to have higher prostate-specific antigen (PSA) levels, Gleason score, risk stratification, and incidence of metastasis.[5,6] Thurner *et al*[7] demonstrated a significant association between elevated plasma fibrinogen levels and poor prognosis of PCa patients who underwent radiotherapy. Moreover, Ziaran *et al*[8] detected a significant increase in fibrinogen levels in PCa patients, after 12 months of androgen deprivation therapy (ADT), which was associated with tolerance of ADT and a poor prognosis. Wang *et al*[6] also reported that the pre-treatment levels of plasma fibrinogen are positively associated with cancer progression in PCa patients treated with ADT.

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Correspondence to: Prof. Gang Li, Department of Urology, The First Affiliated Hospital of Soochow University, 899 Pinghai Road, Suzhou, Jiangsu 215031, China
E-Mail: gangli@suda.edu.cn

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Currently, many advances in metastatic PCa treatment have been accomplished. It has been proved that the combination of chemotherapy, abiraterone, and radiotherapy with ADT can lead to more survival benefits than ADT treatment only.[9-11] However, a proper evaluation of patients' metastatic burden, before treatment, is still necessary since it helps to guide the choice of treatment plan and prognosis.[9,11] So far, rare studies have focused on the association between pre-treatment fibrinogen level and the metastatic burden in PCa. Therefore, here we designed a retrospective study to characterize this potential association.

Methods

Ethics approval

This study was conducted in accordance with the *Declaration of Helsinki*. It was approved by the Ethics Committee of the First Affiliated Hospital of the Soochow University ([2019] No. 531). All participants signed an informed written consent to participate in this study.

Patients

Data from 289 PCa patients, diagnosed by prostate biopsy in the Urology Department of our hospital, from January 2014 to January 2018, were retrospectively collected and analyzed. The inclusion criteria of the study are the following: (i) pathological diagnosis of prostatic adenocarcinoma; (ii) no history of stroke or myocardial infarction; (iii) single-photon emission computed tomography-computed tomography (SPECT-CT) performed shortly after diagnosis of PC (within 2 weeks); (iv) acquisition of multiparameter contrast pelvic magnetic resonance imaging (MRI) before prostate biopsy (within 1 month); (v) plasma PSA and fibrinogen results/data available before prostate biopsy (within 2 weeks). A total of 261 patients met these criteria and were further enrolled in the study.

Clinical and pathological evaluation

All prostate biopsies were guided by ultrasound sonography and performed by the same urologist. A total of 211 patients underwent transrectal biopsy, while the remaining 50 cases underwent transperineal ultrasound-MRI fusion biopsy. Both methods included systemic 12-core puncture, where 1 to 2 needles were added if a suspicious nodule or area was found. Gleason scores were retrieved from respective pathological records. Clinical T staging (cT stage) was evaluated based on MRI, according to the 2002 American Joint Committee on Cancer Tumor, Node, Metastasis staging system. Clinical characteristics including age, plasma PSA, and fibrinogen levels at the time of diagnosis, were collected from our databases.

Bone metastasis was evaluated based on the SPECT-CT results, which were properly reviewed by one selected urologist. In the case of positive detection, the number and location of metastatic lesions were recorded. An isolated condensed radionuclide spot was regarded as one metastatic lesion.

Measurement of blood markers

Plasma PSA and fibrinogen levels were measured shortly before prostate biopsy. After 8-h fasting, patients were submitted to blood drawing. Blood samples (about 3.5 mL) were collected for PSA and fibrinogen analysis. Blood samples for PSA analysis were collected into plastic tubes containing coagulant/separating glue, while fibrinogen detection was performed using blood samples collected into plastic tubes containing 3.8% sodium citrate. PSA was measured using an electrochemiluminescence immunoassay kit (Yuande Bio-Medical Engineering Co. Ltd., Beijing, China), with a normal range of 0 to 4 ng/mL. Fibrinogen was measured by a freezing method, using CS1500coagulation analysis meter (Sysmex Corporation, Kobe, Japan), with a normal range 1.8 to 3.5 g/L.

Group of subjects

According to the burden of bone metastatis, subjects were divided into three groups: non-metastatic group (metastatic lesion = 0), high volume disease (HVD) group (patients with more than three bone metastases and at least one lesion outside spine), and low volume disease (LVD) group (metastatic patients excluding HVD ones). The definitions of HVD and LVD were adopted from the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial.[12] In the study, subjects could be also divided into two groups according to distinct ranges of fibrinogen levels (≤3.5 g/L *vs.* >3.5 g/L, ie, normal plasma fibrinogen *vs.* hyperfibrinogenemia) [Table 1].

Statistical analysis

Due to the non-normal distribution of PSA and fibrinogen levels by frequency analysis, median (percentile) was used.

Table 1: Comparison of clinical parameters between groups presenting distinct ranges of fibrinogen levels (≤3.5 g/L *vs.* >3.5 g/L).

Parameters	Fibrinogen ≤3.5 g/L ($n = 215$)	Fibrinogen >3.5 g/L ($n = 46$)	Statistics	*P*
Age (years)	70 (66, 75)	71 (65, 76)	–0.46*	0.647
PSA (ng/mL)	20.14 (11.75, 59.70)	65.21 (23.50, 121.37)	–3.91*	<0.001
T stage (T1–2/T3–4)	164/51	21/25	207.39†	<0.001
Gleason score (≤7/>7)	114/101	14/32	113.21†	<0.001
Metastatic patients	57 (26.5)	25 (54.3)	187.72†	<0.001
HVD patients	21 (9.8)	17 (40.0)	339.87†	<0.001

Data are presented as median (P25, P75), *n/n*, or *n* (%). * *Z* values. † χ^2 values. HVD: High volume disease; PSA: Prostate-specific antigen; T: Tumor.

The non-parametric Mann-Whitney test was used to compare group parameters. Dual-parameter correlation was analyzed by the Spearman method. Categorical variables were counted as numbers (percentage), and Chi-square was used for comparison between groups. Univariate and multivariate logistic regression analysis were performed to evaluate the association between each parameter with the status of bone metastasis. To establish fibrinogen cut-off values, a receiver operating characteristic (ROC) curve was plotted and the resulting area under the curve (AUC) was calculated. The value with the largest Youden index [calculated as (sensitivity + specificity) − 1] was defined as the optimal cut-off value. All tests were two-sided. Differences were considered to be statistically significant if $P < 0.05$. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

The basic characteristics of the patient cohort are given in Table 2. Since only a few patients in this study underwent positron emission tomography (PET-CT) or whole-body CT and, consequently, visceral metastases could not be assessed, we solely evaluated bone metastases. A total of 82 patients presented bone metastasis (metastatic lesion number ranged from 1 to 33).

Association between fibrinogen and clinical characteristics

A significant positive correlation between fibrinogen and Gleason score ($r = 0.180$, $P = 0.003$), PSA ($r = 0.216$, $P < 0.001$), or the number of metastatic lesions ($r = 0.296$, $P < 0.001$) was observed. No significant correlation between fibrinogen and age ($r = 0.042$, $P = 0.503$), cT stage ($r = 0.104$, $P = 0.093$), or positive cores ($r = 0.065$, $P = 0.308$) was detected. A higher PSA level ($P < 0.001$), more high-risk cancers (ie, cT3–4 stage or Gleason score >7; $P < 0.001$), and more HVD ($P < 0.001$) were identified in the patients with fibrinogen >3.5 g/L when compared with the ones with fibrinogen ≤3.5 g/L [Table 1].

Comparative analysis of plasma fibrinogen according to patient metastatic status

A parameter comparison between all groups is shown in Table 3. No statistical difference in age was observed between any two groups. Compared with the non-metastatic and LVD groups, HVD patients had higher levels of PSA and fibrinogen, increased Gleason score, and more T3–4 stage cancers ($P < 0.05$). However, no statistical difference in fibrinogen levels when comparing the non-metastatic and the LVD groups was detected ($P = 0.076$). Furthermore, we verified that patients with more bone metastases had a higher incidence of fibrinogen levels above 3.5 g/L ($P < 0.001$).

Association between fibrinogen levels and HVD

Since PSA was distributed in a large range with a non-normal distribution, respective data were transformed to natural logarithm before analysis. Both univariate and multivariate logistic regressions showed that, with statistical significance, fibrinogen is independently associated with HVD [Table 4]. The ROC curve could demonstrate that the sensitivity and specificity were 0.684 and 0.760, respectively, when fibrinogen was 3.08 g/L (AUC = 0.739; 95% confidential interval: 0.644–0.833; $P < 0.001$) [Figure 1].

Table 2: Clinical characteristics of selected PCa patients ($n = 261$).

Parameters	Values
Age (years)	70 (66, 75)
PSA (ng/mL)	27.06 (12.42, 78.72)
Fibrinogen (g/L)	2.62 (2.20, 3.24)
Positive cores	7 (3, 11)
Gleason score	
<7	42 (16.1)
7	86 (33.0)
>7	133 (50.9)
No. of bone metastasis	
0	179 (68.6)
1–3	44 (16.9)
>3	38 (14.5)
Clinical stage	
T1	26 (9.9)
T2	160 (61.3)
T3	50 (19.2)
T4	25 (9.6)

Data are presented as median (P25, P75) or *n* (%). PCa: Prostate cancer; PSA: Prostate-specific antigen; T: Tumor.

Table 3: Comparison of clinical parameters among non-metastatic (Group 1), LVD (Group 2), and HVD group (Group 3).

Parameters	Group 1 ($n = 179$)	Group 2 ($n = 44$)	Group 3 ($n = 38$)	*P*1 (sta)	*P*2 (sta)	*P*3 (sta)
Age (years)	70 (65, 75)	71 (68, 75)	71.5 (66, 77)	0.248 (–1.16*)	0.193 (–1.30*)	0.759 (–0.31*)
PSA (ng/mL)	19.84 (10.47, 47.37)	47.80 (16.41, 92.00)	104.98 (73.64, 177.26)	0.003 (–2.93*)	<0.001 (–6.64*)	<0.001 (–3.71*)
Fibrinogen (g/L)	2.50 (2.07, 2.97)	2.67 (2.36, 3.29)	3.39 (2.68, 4.39)	0.076 (–1.78*)	<0.001 (–4.82*)	0.002 (–3.03*)
T stage (T1–2/T3–4)	145/34	30/14	11/27	<0.001 (194.53†)	<0.001 (207.54†)	0.005 (12.93†)
Gleason score (≤7/>7)	106/73	17/27	5/33	<0.001 (92.39†)	<0.001 (108.88†)	0.001 (22.00†)
Fibrinogen >3.5 g/L	21 (11.7)	9 (20.5)	17 (44.7)	<0.001 (256.12†)	<0.001 (264.75†)	0.001 (17.32†)

Data are presented as median (P25, P75), *n*/*n*, or *n* (%). *Z values; †χ^2 values. LVD: Low volume disease; HVD: High volume disease; *P*1: Group 1 *vs.* group 2; *P*2: Group 1 *vs.* group 3; *P*3: Group 2 *vs.* group 3; sta: Statistics; PSA: Prostate-specific antigen; T: Tumor.

Table 4: Univariate and multivariate logistic regression analysis of selected parameters in HVD patients.

Parameters	Univariate regression			Multivariate regression		
	P	OR	95% CI of OR	*P*	OR	95% CI of OR
PSA logarithm	<0.001	2.009	1.620–2.492	0.018	1.808	1.109–2.946
Fibrinogen	<0.001	2.160	1.536–3.038	0.003	1.726	1.206–2.472
T stage	<0.001	3.003	1.832–4.922	0.001	2.334	1.390–3.918
Gleason score	<0.001	2.369	1.631–3.441	0.036	1.592	1.030–2.460

HVD: High volume disease; OR: Odds ratio; CI: Confidential interval; PSA: Prostate-specific antigen; T: Tumor.

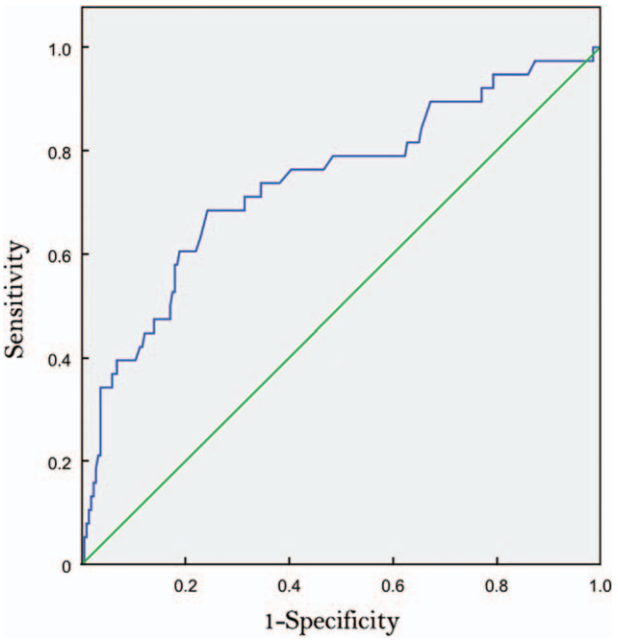

Figure 1: ROC curve of fibrinogen in HVD patients. The ROC curve could assess fibrinogen as a satisfying marker of HVD diagnosis, yielding a cut-off of 3.08 g/L, with a sensitivity of 0.684 and a specificity of 0.760 (AUC = 0.739, 95% CI: 0.644–0.833, $P < 0.001$). AUC: Area under curve; CI: Confidential interval; HVD: High volume disease; ROC: Receiver operating characteristic.

Discussion

As an acute-phase protein, the yields of plasma fibrinogen typically increase during cancer progression, systemic inflammation, trauma, surgery, and blood vessel thromboembolism.[13] Previous studies have reported that fibrinogen levels are positively correlated with T staging, Gleason score, risk stratification, and metastasis in PCa.[5,6] Moreover, increase in plasma fibrinogen levels has been considered an unfavorable prognostic indicator in both radiotherapy and ADT. Nevertheless, no major research that could strengthen the relationship between fibrinogen levels and bone metastatic status has been developed, up to now. Therefore, here we present the association analysis between fibrinogen and metastatic burden, in the context of PCa.

In PCa, the distinction between HVD and LVD is clinically significant. LVD has been named oligo-metastasis in a number of studies. Many clinical trials have found that the number of metastatic lesions is associated with cancer prognosis. Patients with metastases, including less than five lesions, have a significantly better cancer-specific survival than those with more metastatic lesions.[14] Therefore, local therapy for patients with primary cancer and limited number of metastatic lesions, in combination with ADT, has been largely recommended.[15] Heidenreich *et al*[16] have reported that radical prostatectomy provides a better clinical progression-free survival (38.6 *vs*. 26.5 months, $P = 0.032$) and cancer-specific survival rates (95.6% *vs*. 84.2%, $P = 0.043$) in PCa patients with no more than three bone metastases. The CHAARTED trial has shown that docetaxel-based chemotherapy had survival benefits for HVD patients.[9] On the other hand, radiotherapy improved the survival of LVD patients in the Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: a multi-stage multi-arm randomised control trial (STAMPEDE) trial.[11]

Still, there is not a current widely-accepted definition for HVD and LVD. According to former clinical trials, the cut-off of 3 to 5 lesions has been used to distinguish these categories.[17-20] However, these differences do not affect clinical applications. In this regard, the definitions of CHAARTED and LATITUDE trials are consistent, and both trials have added significant prognostic value for predicting overall survival.[21] In this study, we adopted the definition of CHAARTED trial.

SPECT-CT is the most commonly used radiological method to diagnose PCa bone metastasis. A meta-analysis has reported that its sensitivity and specificity can reach 79% and 82%, respectively.[22] Multi-parameter MRI (mpMRI) is also clinically available. Another meta-analysis has indicated that the diagnostic sensitivity and specificity of mpMRI for bone metastasis, during initial PCa diagnosis, were 0.93 and 0.99, respectively.[23] In contrast, fluorodeoxyglucose (FDG) -PET/CT has not been routinely used to diagnose bone metastasis, since it has a relatively poorer accuracy when compared with SPECT-CT or MRI.[24] However, new radiotracers may provide a more efficient and sensitive imaging, such as prostate-specific membrane antigen (PSMA).[25] Indeed, a systemic review has recently indicated that ^{68}Ga-PSMA PET/CT could more efficiently detect osseous metastases than SPECT-CT.[26]

Our research has revealed that plasma fibrinogen levels are significantly higher in HVD patients than in non-metastatic or LVD ones. Multivariate regression analysis has proven that fibrinogen is independently associated with HVD.

There are several hypothetical mechanisms of how fibrinogen may enhance the progression and metastatic potential of PCa. First, fibrinogen may gather around tumors to provide a framework for tumor cell proliferation. Fibrinogen can serve as a scaffold to support certain growth factors, such as vascular endothelial growth factor and fibroblast growth factor, to promote tumor angiogenesis.[13] Second, tumor cells contain fibrinogen receptors, which play a role in bridging fibrinogen molecules to tumor cells, thus enhancing the endothelial adhesion of tumor cell emboli in the vasculature of target organs. This event will lead to the occurrence of metastasis and potentially increase the survival rates of early metastatic cells.[27] Third, fibrinogen can enhance the adhesion of platelets into tumor cells, mediated by β3-integrin (expressed by tumor cells). Platelets can promote the aggregation of fibrinogen around the tumor cell environment. As a result, a dense fibrin layer may be formed to provide protection to tumor cells against natural killer cells, leading to a higher probability of remote metastasis.[28] Moreover, PCa cells can synthesize fibrinogen endogenously which may lead to a proliferative and angiogenic effect, driven by fibroblast growth factor-2, and the induction of PCa progression and metastasis.[29]

It is worth noting that HVD patients typically display higher fibrinogen levels in the blood. In fact, we presently observed that 44.7% of HVD patients showed levels higher than 3.5 g/L. A high fibrinogen level is a known risk factor for many cardiovascular conditions, particularly in coronary heart disease.[30,31] Therefore, a prophylactic anti-coagulation treatment is highly advisable for these patients.

Nevertheless, a few limitations should be considered in this study. First, our work corresponds to a single-center retrospective study, so some statistically selective bias may be assumed. Second, despite our strict enrollment criteria, we were unable to completely exclude other conditions that might affect plasma fibrinogen levels, such as varicose vein of lower limb, atherosclerosis, and others. Third, although SPECT-CT is regarded as the "gold standard" for the detection of skeletal metastases in PCa patients, this platform could still lead an incorrect diagnosis. Fourth, since our focus was mainly to determine the number and location of bone metastatic lesions displayed by SPECT-CT, we did not calculate the size or the dimension of affected areas. Bone scan index[32] as a means of estimating the percentage of tumors along the whole skeleton could be considered to better distinguish PCa-related metastatic conditions. Lastly, visceral metastasis was not assessed, and this condition may have been missed in some HVD patients. Multi-center prospective studies, including larger sample sizes, will be further required to confirm the results of this study.

In conclusion, pre-treatment plasma fibrinogen levels are positively correlated with bone metastatic numbers, but it is independently associated with HVD. These results validate an alternate route of assessment (ie, fibrinogen levels in the blood) as a putative marker for more precise diagnosis and treatment of advanced PCa.

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Conflicts of interest

None.

References

1. Lyman GH, Khorana AA. Cancer, clots and consensus: new understanding of an old problem. J Clin Oncol 2009;27:4821–4826. doi: 10.1200/JCO.2009.22.3032.
2. Lollar P. Pathogenic antibodies to coagulation factors. Part II. Fibrinogen, prothrombin, thrombin, factor V, factor XI, factor XII, factor XIII, the protein C system and von Willebrand factor. J Thromb Haemost 2005;3:1385–1391. doi: 10.1111/j.1538-7836.2005.01228.x.
3. Wen J, Yang Y, Ye F, Huang X, Li S, Wang Q, *et al*. The preoperative plasma fibrinogen level is an independent prognostic factor for overall survival of breast cancer patients who underwent surgical treatment. Breast 2015;24:745–750. doi: 10.1016/j.breast.2015.09.007.
4. Allin KH, Bojesen SE, Nordestgaard BG. Inflammatory biomarkers and risk of cancer in 84,000 individuals from the general population. Int J Cancer 2016;139:1493–1500. doi: 10.1002/ijc.30194.
5. Alevizopoulos A, Tyritzis S, Leotsakos I, Anastasopoulou I, Pournaras C, Kotsis P, *et al*. Role of coagulation factors in urological malignancy: a prospective, controlled study on prostate, renal and bladder cancer. Int J Urol 2017;24:130–136. doi: 10.1111/iju.13271.
6. Wang Y, Yin W, Wang Z, Huang J, Pan J, Zhu Y, *et al*. Pretreatment plasma fibrinogen as an independent prognostic indicator of prostate cancer patients treated with androgen deprivation therapy. Prostate Cancer Prostatic Dis 2016;19:209–215. doi: 10.1038/pcan.2016.6.
7. Thurner EM, Krenn-Pilko S, Langsenlehner U, Stojakovic T, Pichler M, Gerger A, *et al*. The association of an elevated plasma fibrinogen level with cancer-specific and overall survival in prostate cancer patients. World J Urol 2014;33:1467–1473. doi: 10.1007/s00345-014-1459-2.
8. Ziaran S, Goncalves FM, Breza J Sr. Patients with prostate cancer treated by ADT have significantly higher fibrinogenemia than healthy control. World J Urol 2013;31:289–292. doi: 10.1007/s00345-012-0926-x.
9. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, *et al*. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080–1087. doi: 10.1200/JCO.2017.75.3657.
10. Rydzewska LHM, Burdett S, Vale CL, Clarke NW, Fizazi K, Kheoh T, *et al*. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. Eur J Cancer 2017;84:88–101. doi: 10.1016/j.ejca.2017.07.003.
11. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, *et al*. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet 2018;392:2353–2366. doi: 10.1016/S0140-6736(18)32486-3.
12. Gravis G, Boher JM, Joly F, Soulié M, Albiges L, Priou F, *et al*. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non-castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 Trial. Eur Urol 2016;70:256–262. doi: 10.1016/j.eururo.2015.11.005.
13. Caliskan S, Sungur M. Fibrinogen and D-dimer levels in prostate cancer: preliminary results. Prostate Int 2017;5:110–112. doi: 10.1016/j.prnil.2017.05.001.
14. Singh D, Yi WS, Brasacchio RA, Muhs AG, Smudzin T, Williams JP, *et al*. Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int J Radiat Oncol 2004;58:3–10. doi: 10.1016/S0360-3016(03)01442-1.
15. Aoun F, Peltier A, van Velthoven R. A comprehensive review of contemporary role of local treatment of the primary tumor and/or the metastases in metastatic prostate cancer. Biomed Res Int 2014;2014:501213. doi: 10.1155/2014/501213.

16. Heidenreich A, Pfister D, Porres D. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. J Urol 2015;193:832–838. doi: 10.1016/j.juro.2014.09.089.
17. Berkovic P, De Meerleer G, Delrue L, Lambert B, Fonteyne V, Lumen N, *et al*. Salvage stereotactic body radiotherapy for patients with limited prostate cancer metastases: deferring androgen deprivation therapy. Clin Genitourin Cancer 2013;11:27–32. doi: 10.1016/j.clgc.2012.08.003.
18. Decaestecker K, De Meerleer G, Lambert B, Delrue L, Fonteyne V, Claeys T, *et al*. Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. Radiat Oncol 2014;9:135. doi: 10.1186/1748-717X-9-135.
19. Ost P, Jereczek-Fossa BA, As NV, Zilli T, Muacevic A, Olivier K, *et al*. Progression-free survival following stereotactic body radiotherapy for oligometastatic prostate cancer treatment-naive recurrence: a multi-institutional analysis. Eur Urol 2016;69:9–12. doi: 10.1016/j.eururo.2015.07.004.
20. Tabata K, Niibe Y, Satoh T, Tsumura H, Ikeda M, Minamida S, *et al*. Radiotherapy for oligometastases and oligo-recurrence of bone in prostate cancer. Pulm Med 2012;2012:541656. doi: 10.1155/2012/541656.
21. Sarah Buelens , Filip Poelaert , Bert Dhondt , Fonteyne V, De Visschere P, Ost P, *et al*. Metastatic burden in newly diagnosed hormone-naïve metastatic prostate cancer: comparing definitions of CHAARTED and LATITUDE trial. Urol Oncol 2018;36:13–20. doi: 10.1016/j.urolonc.2017.12.009.
22. Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. Skeletal Radiol 2014;43:1503–1513. doi: 10.1007/s00256-014-1903-9.
23. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic performance of magnetic resonance imaging for the detection of bone metastasis in prostate cancer: a systematic review and meta-analysis. Eur Urol 2018;73:81–91. doi: 10.1016/j.eururo.2017.03.042.
24. Ghanem N, Uhl M, Brink I, Schäfer O, Kelly T, Moser E, *et al*. Diagnostic value of MRI in comparison to scintigraphy, PET, MSCT and PET/CT for the detection of metastases of bone. Eur J Radiol 2005;55:41–55. doi: 10.1016/j.ejrad.2005.01.016.
25. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA-PET in prostate cancer management. Nat Rev Urol 2016;13:226–235. doi: 10.1038/nrurol.2016.26.
26. Zacho HD, Nielsen JB, Haberkorn U, Stenholt L, Petersen LJ. 68Ga-PSMA PET/CT for the detection of bone metastases in prostate cancer: a systematic review of the published literature. Clin Physiol Funct Imaging 2017;29:5–12. doi: 10.1111/cpf.12480.
27. Yano HJ, Hatano K, Tsuno N, Osada T, Watanabe T, Tsuruo T, *et al*. Clustered cancer cells show a distinct adhesion behavior from single cell form under physiological shear conditions. J Exp Clin Cancer Res 2001;20:407–412. doi: 10.1007/s004320100259.
28. Bagoly Z. Cancer and thrombosis: a fresh look at an old story. Thromb Res 2015;136:1–2. doi: 10.1016/j.thromres.2015.04.028.
29. Thurner EM, Pilko SK, Langsenlehner U, Stojakovic T, Pichler M, Gerger A, *et al*. The association of an elevated plasma fibrinogen level with cancer specific and overall survival in prostate cancer patients. World J Urol 2015;33:1467–1473. doi: 10.1007/s00345-014-1459-2.
30. Mjelva OR, Svingen GFT, Pedersen EKR, Seifert R, Kvaløy JT, Midttun Ø, *et al*. Fibrinogen and neopterin is associated with future myocardial infarction and total mortality in patients with stable coronary artery disease. Thromb Haemost 2018;118:778–790. doi: 10.1055/s-0038-1629912.
31. Gao XY, Zhou BY, Zhang MZ, Zhao X, Qing P, Zhu CG, *et al*. Association between fibrinogen level and the severity of coronary stenosis in 418 male patients with myocardial infarction younger than 35 years old. Oncotarget 2017;8:81361–81368. doi: 10.18632/oncotarget.18578.
32. Nakajima K, Edenbrandt L, Mizokami A. Bone scan index: a new biomarker of bone metastasis in patients with prostate cancer. Int J Urol 2017;24:668–673. doi: 10.1111/iju.13386.

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