World J Urol (2015) 33:1467–1473
DOI 10.1007/s00345-014-1459-2

ORIGINAL ARTICLE

The association of an elevated plasma fibrinogen level with cancer-specific and overall survival in prostate cancer patients

Eva-Maria Thurner · Sabine Krenn-Pilko · Uwe Langsenlehner · Tatjana Stojakovic · Martin Pichler · Armin Gerger · Karin S. Kapp · Tanja Langsenlehner

Received: 11 August 2014 / Accepted: 28 November 2014 / Published online: 5 December 2014

Abstract
Purpose Fibrinogen plays an important role in the pathophysiology of tumour cell invasion and metastases. In recent studies, an elevated plasma fibrinogen level has been associated with poor prognosis in different types of cancer. The present study was performed to analyse the prognostic impact of an elevated fibrinogen level in prostate cancer patients.
Methods We evaluated data from 268 prostate cancer patients who underwent 3D conformal radiotherapy between 1999 and 2006 at a single tertiary academic center. Cancer-specific survival (CSS), overall survival (OS), and clinical disease-free survival (DFS) were assessed using the Kaplan–Meier method. Univariable and multivariable Cox regression models were performed for each endpoint.
Results Applying receiver operating characteristics (ROC) curve analysis, the optimal cut-off level for the plasma fibrinogen level was 530 mg dl^{-1}, respectively. Univariable (HR 3.638, 95 % CI 1.15–11.47, $p = 0.027$) and multivariable analyses (HR 3.964, 95 % CI 1.06–14.87, $p = 0.041$) revealed a significant correlation between increased plasma fibrinogen and CSS. Univariable analysis also showed a significant association between the elevated plasma fibrinogen level and decreased OS (HR 3.242, 95 % CI 1.53–6.89, $p = 0.002$), that remained significant in multivariable analysis (HR 3.215, 95 % CI 1.44–7.19, $p = 0.004$). No significant associations were found for clinical DFS.
Conclusion Although our data show a significant association between an elevated plasma fibrinogen level and poor prostate cancer prognosis, they have to be interpreted cautiously. Limitations of the present study are caused by its retrospective design, the limited accuracy obtained using ROC curve analysis, and potential confounding factors like cardiovascular disease and inflammatory diseases that have not been accounted for.

Keywords Prostate cancer · Radiotherapy · Prognosis · Coagulation · Fibrinogen

E.-M. Thurner · S. Krenn-Pilko · K. S. Kapp · T. Langsenlehner (✉)
Department of Therapeutic Radiology and Oncology, Comprehensive Cancer Center Graz, Medical University of Graz, Auenbruggerplatz 32, 8036 Graz, Austria
e-mail: tanja.langsenlehner@medunigraz.at

U. Langsenlehner
Division of Internal Medicine, Outpatient Department Graz, Graz, Austria

T. Stojakovic
Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria

M. Pichler · A. Gerger
Division of Clinical Oncology, Department of Medicine, Medical University of Graz, Graz, Austria

Introduction

Prostate cancer is the second most common cancer in men worldwide [1]. The routine diagnostic and prognostic assessment currently relies on clinicopathological prognostic variables such as Gleason score, clinical tumour stage, and prostate-specific antigen (PSA) level at the time of diagnosis that are used for the patients' assignment into the low-, intermediate-, or high-risk group. The accuracy of traditional prognostic models might be further improved by the incorporation of prognostic biomarkers.

There is rising evidence that supports an interactive relationship between haemostatic factors and tumour biology

[2]. Procoagulant factors are overexpressed in several tumours and have been found to influence tumour growth and progression, angiogenesis, and metastatic spread of malignant cells [3–8].

Fibrinogen, a 340-kDa glycoprotein, is one of the most important coagulation factors and has previously been evaluated in several types of cancer. It has been shown to be a critical determinant of the metastatic potential of circulating tumour cells in lung carcinoma and melanoma [9]. Furthermore, elevated pre-treatment plasma fibrinogen levels have been associated with poor clinical outcome in various malignancies [10–18].

However, data regarding the prognostic significance of the plasma fibrinogen levels in prostate cancer are sparse. The aim of the present study was to investigate the prognostic value of fibrinogen levels on CSS, OS, and clinical DFS in a cohort in European prostate cancer patients.

Materials and methods

Subjects

An institutional database of more than 700 patients with histologically confirmed prostate cancer who attended the Department of Therapeutic Radiology and Oncology, Medical University of Graz, during the years 1999 through 2006 was analysed. Eligible for inclusion in the present analysis were male patients with histologically confirmed prostate cancers who had fibrinogen levels recorded for any reason and underwent radiation therapy for prostate cancer.

Applying the criteria mentioned above, a total of 268 patients were included in the present analysis. Data on clinical characteristics including prostate-specific antigen (PSA) at the time of diagnosis, tumour node metastasis (TNM) stage, histological grade, age at diagnosis, and causes of death were retrieved from electronic patient records of our institution.

Eligible patients were treated with three-dimensional conformal radiation therapy using high-energy photons (18 MV). The median total dose was 70 Gy (range 66–74 Gy) delivered in 1.8–2.0 Gy per fraction. A total of 165 patients (61.6 %) received neoadjuvant androgen deprivation, and 56 patients (20.9 %) received adjuvant hormonal therapy, respectively. Prostate cancer patients were stratified into low-, intermediate-, and high-risk groups on the basis of pre-treatment PSA level, Gleason score (GS), and T-stage. The patients were classified as high risk if they met any of the following criteria: T3–4, or GS 8–10, or PSA > 20 ng ml^{-1}. The intermediate-risk group included stages T2b–2c, GS 7, or PSA 10–20 ng ml^{-1}; the low-risk group contained stages T1–T2a, GS $\leq$ 6, and PSA < 10 ng ml^{-1}.

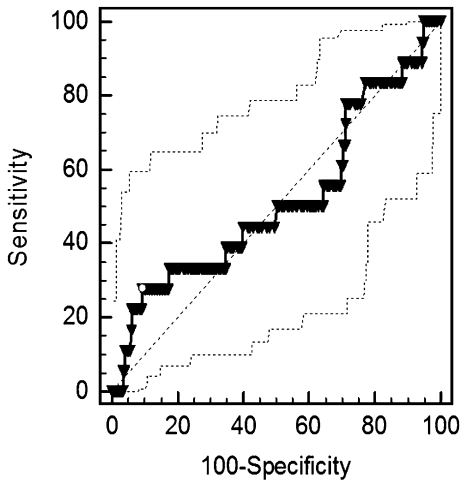

Fig. 1 ROC analysis of optimal fibrinogen cut-off level

Fibrinogen levels were usually measured as part of routine clinical evaluation prior to the start of radiotherapy. In case of neoadjuvant androgen derivation therapy, fibrinogen levels obtained prior to the start of androgen deprivation have been used for analysis. Plasma fibrinogen levels were determined at a certified center by the Clauss method by using reagents, standards, and control plasma from Dade Behring on a BCS analyzer (Dade Behring, Marburg, Germany). The inter-assay coefficient of variation was <3 and <7.5 % for the plasma control in the normal and pathological range, respectively.

Follow-up examinations included PSA measurements and digital rectal examinations (3 months interval in years 1–3, 6 months interval in years 4–5, and 12 months interval in years 6–15 after diagnosis). Patients with PSA relapse, defined as a rise by $\geq$2 ng ml^{-1} above the nadir PSA, were regularly checked through diagnostic tests, comprising isotope bone scan, chest X-ray, and abdominal and pelvic computed tomography as well as magnetic resonance imaging studies to detect local recurrences and/or distant metastases.

Statistical analysis

The primary study endpoint was CSS, defined as the time from prostate cancer diagnosis to prostate cancer-related death. The secondary endpoints included OS, calculated from date of diagnosis to death of any cause, and clinical DFS, which was defined as the time from prostate cancer diagnosis to the occurrence of local recurrence and/or distant metastases. The cut-off value for the continuous variable plasma fibrinogen level was determined by applying a receiver operating characteristics (ROC) curve analysis to test all possible cut-offs that would separate between patients' survival and cancer-related death (Fig. 1).

Nonparametric tests (Chi-square tests) were used to analyse the relationship between plasma fibrinogen levels and other clinicpathological features. Clinical endpoints were analysed using the Kaplan–Meier method and were compared by the log-rank test. Multivariable Cox proportion analysis was performed to determine the influence of potential confounders such as age, additional hormonal therapy, risk group based on T-stage, PSA level at diagnosis, and Gleason score on CSS, OS and clinical DFS. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95 % confidence intervals (CIs). Statistical analyses were performed using the IBM SPSS Statistic software package version 20.0 (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered to be significant.

Results

Details on patient characteristics are shown in Table 1. Applying the criteria mentioned above, a plasma fibrinogen cut-off value of 530 mg dl^{-1} was optimal for the discrimination between patients' CSS and for all further analyses this cut-off value was used to differentiate between low (<530) and high (≥530) fibrinogen levels. A high fibrinogen level did not significantly correlate with age at diagnosis, tumour stage, Gleason score, PSA level at first diagnosis, and risk group (all $p > 0.05$, data not shown).

Mean follow-up time was 88 months (95 % CI 83.3–92.7 months). Of the 268 prostate cancer patients, 42 (15.7 %) developed clinical recurrences. Death from prostate cancer occurred in 15 patients (5.6 %) who had developed extensive metastases. In all of them, tumour burden was judged as the immediate cause of death. Overall, 37 patients (13.8 %) died from any cause.

In Kaplan–Meier analysis, high plasma fibrinogen levels were significantly associated with poor CSS ($p = 0.018$; Fig. 2) and OS ($p = 0.001$; Fig. 3), but not with clinical DFS ($p = 0.139$).

In univariable analysis, a high plasma fibrinogen level was a poor prognostic marker for CSS (HR 3.638, 95 % CI 1.15–11.47, $p = 0.027$; Table 2) and in a subsequent multivariable analysis including age, risk group, and antihormonal treatment as potential confounders, a high fibrinogen level remained a significant prognostic factor (HR 3.964, 95 % CI 1.06–14.87, $p = 0.041$; Table 2). Moreover, we observed a significant correlation between increased plasma fibrinogen and OS in univariable (HR 3.242, 95 % CI 1.53–6.89, $p = 0.002$; Table 3) and in multivariable analysis (HR 3.215, 95 % CI 1.44–7.19, $p = 0.004$; Table 3). No significant associations were found for the secondary endpoint clinical DFS in univariable (HR 1.910, 95 % CI 0.780–4.57, $p = 0.147$) as well as in multivariable analysis (HR 2.418, 95 % CI 0.92–6.38, $p = 0.074$).

Table 1 Patient characteristics

	Patient characteristics
n	268
Age at diagnosis, years (mean ± SD)	66.9 ± 7.5
PSA at first diagnosis (ng ml^{-1})	
0–10	129 (48.1 %)
10–20	71 (26.5 %)
>20	56 (20.9 %)
Missing data	12 (4.6 %)
Tumour stage	
T1/2	139 (51.9 %)
T3/4	116 (43.3 %)
Missing data	13 (4.9 %)
Gleason score	
Gleason <7	166 (61.9 %)
Gleason ≥7	102 (38.1 %)
Risk group	
Low risk	52 (19.4 %)
Intermediate risk	62 (23.1 %)
High risk	154 (57.5 %)
Neoadjuvant androgen deprivation	
Yes	165 (61.6 %)
No	103 (38.4 %)
Adjuvant androgen deprivation	
Yes	56 (20.9 %)
No	212 (79.1 %)
Fibrinogen plasma level (mg dl^{-1})	
<530	236 (88 %)
≥530	32 (12 %)

n number of patients, *SD* standard deviation

Discussion

The data from the present study show a significant association between an elevated plasma fibrinogen level and poor CSS and OS in prostate cancer patients that was independent of patient age, adjuvant and neoadjuvant androgen deprivation, and risk group that is based on tumour stage, grading, and PSA level at diagnosis.

In cancer patients, elevated fibrinogen levels may be caused by tumour-associated cytokines or by an increased synthesis of fibrinogen by tumour cells themselves. The endogenously produced fibrinogen has been found to promote the growth of lung and prostate cancer cells through interaction with fibroblast growth factor 2 [5].

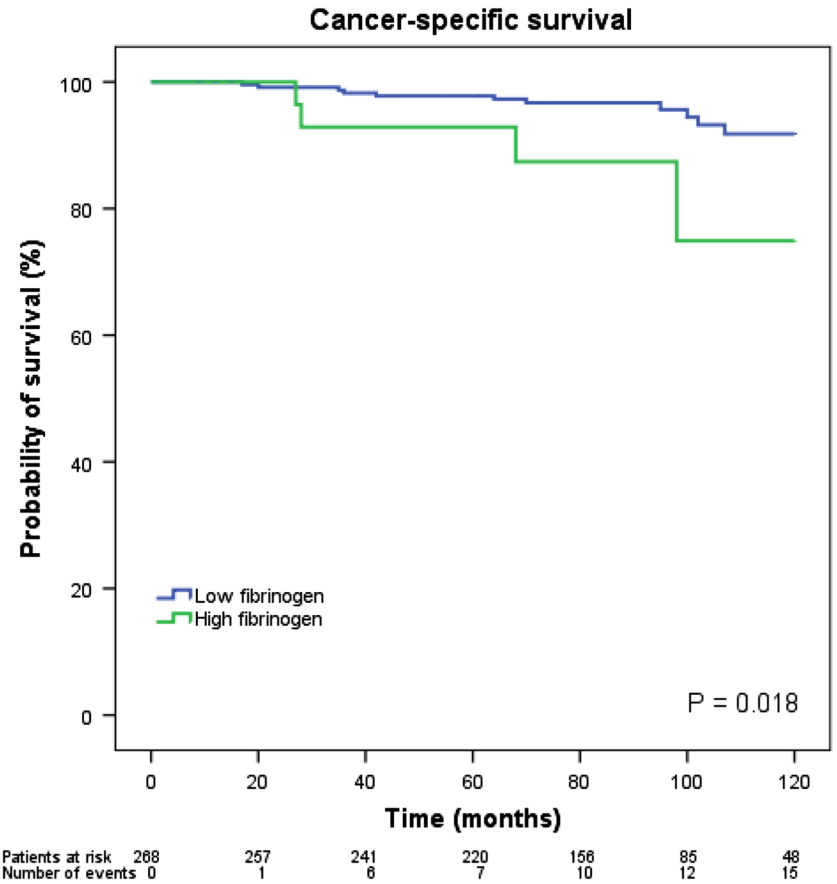

Fig. 2 Kaplan–Meier curves for cancer-specific survival of prostate cancer patients categorised by the plasma fibrinogen level

Fibrinogen has also been shown to act as a bridging molecule between tumour cells and the surrounding microenvironment. Zheng et al. demonstrated that fibrinogen enhances the adhesion of platelets to tumour cells mediated by β3-integrins that are expressed on human cancer cells. In turn, platelets promote the aggregation of fibrinogen around tumour cells leading to the formation of dense fibrin layers that facilitate the protection of tumour cells from natural killer cell elimination [19]. The importance of the interaction between cancer cell-expressed integrins and fibrinogen has also been demonstrated in an inflammation-driven animal cancer model of colorectal cancer by Steinbrecher et al. [20].

Two previous studies have previously addressed the role of hyperfibrinogenemia in prostate cancer. Ziaran et al. [21] demonstrated a significant increase of fibrinogen levels in prostate cancer patients after 12 months of androgen deprivation therapy. In contrast, Seal and colleagues showed a significant decrease of fibrinogen levels after treatment with estrogens in patients stage III and IV prostate cancer. Additionally, the authors reported a significant correlation of elevated pre-treatment fibrinogen levels with overall mortality and a trend for an association between elevated fibrinogen levels and prostate cancer mortality [22].

McDonald and colleagues have analysed the association between fibrinogen and serum PSA levels in men without clinical prostate disease. The authors reported a positive relationship between fibrinogen and elevated serum PSA level suggesting that an elevated fibrinogen level may contribute to the characterisation of a subgroup of men at higher risk for prostate cancer [23].

The findings from the present study are in line with data from recent studies showing a poor outcome in cancer patients with increased plasma fibrinogen levels [10–18]. Cancer patients with an elevated plasma fibrinogen level might be considered as candidates for additional, more aggressive treatment approaches or more stringent follow-up schedules.

However, our data have to be regarded as preliminary and have to be interpreted cautiously.

There are some limitations that have to be taken into account. Using ROC curve analysis, we determined a cut-off value of 530 mg dl^{-1} for the plasma fibrinogen level to be optimal to discriminate between the patients' CSS. However, the generated ROC curve suggests a limited ability of our test to correctly classify patients with and without cancer-related death. It is therefore questionable if a cut-off value of 530 will be a useful predictor of the patients´ outcome and its validation in additional studies is necessary.

Furthermore, because of the retrospective study design, we are unable to exclude the possibility that an unequal

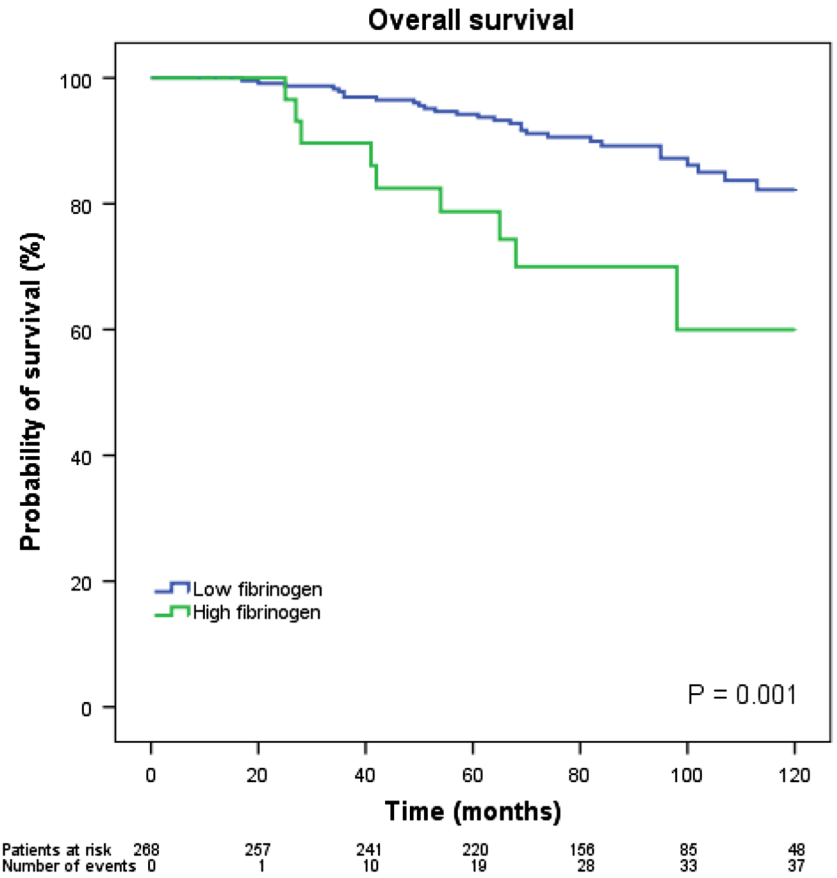

Fig. 3 Kaplan–Meier curves for overall survival of prostate cancer patients categorised by the plasma fibrinogen level

Table 2 Univariable and multivariable Cox proportional analysis of clinical parameters for the prediction of cancer-specific survival in prostate cancer patients

Parameter	Univariable analysis		Multivariable analysis[a]	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age at diagnosis (years)	0.988 (0.92–1.06)	0.733	0.982 (0.90–1.07)	0.677
Risk group (high vs. intermediate vs. low)	6.727 (1.08–41.9)	0.041	6.327 (0.99–40.37)	0.051
(Neo)adjuvant androgen deprivation (yes vs. no)	1.733 (0.47–6.45)	0.412	6.327 (0.55–9.46)	0.253
Fibrinogen plasma level (mg dl^{-1}) (≥530 vs. <530)	3.638 (1.15–11.47)	0.027	3.964 (1.06–14.87)	0.041

CI confidence interval, *HR* hazard ratio

[a] Adjustment for all factors listed in the table

Table 3 Univariable and multivariable Cox proportional analysis of clinical parameters for the prediction of overall survival in prostate cancer patients

Parameter	Univariable analysis		Multivariable analysis[a]	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age at diagnosis (years)	1.027 (0.98–1.07)	0.235	1.02 (0.97–1.08)	0.474
Risk group (high vs. intermediate vs. low)	1.328 (0.85–2.08)	0.216	1.456 (0.91–2.34)	0.121
(Neo)adjuvant androgen deprivation (yes vs. no)	1.862 (0.84–4.13)	0.126	1.829 (0.80–4.21)	0.156
Fibrinogen plasma level (mg dl^{-1}) (≥530 vs. <530)	3.242 (1.53–6.89)	0.002	3.215 (1.44–7.19)	0.004

CI confidence interval, *HR* hazard ratio

[a] Adjustment for all factors listed in the table

distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. As fibrinogen is an important player in the coagulation cascade, high plasma fibrinogen levels might also impair patients' survival by triggering thromboembolism events. The association between high plasma fibrinogen levels and a higher risk of thromboembolism in cancer patients is currently discussed controversially [24, 25]. In our study cohort, only one patient has developed a thromboembolic event; therefore, a significant influence of high plasma fibrinogen levels on patient survival by triggering thromboembolic events can be excluded.

The median follow-up time of our study was 88 months. Prostate cancer recurrences may occur 10–15 years after successful primary treatment; therefore, long-term follow-up of prostate cancer patients is necessary to assess treatment efficacy and survival rates and conclusions from studies with <15 years of follow-up should be viewed as preliminary.

Another limitation might be caused by the radiation dose administered to the patients. At the time of the patients´ treatment, the total dose recommended for prostate cancer radiotherapy was 70 Gy. In more recently published randomised controlled studies, an improved biochemical recurrence-free survival has been found for dose-escalated radiotherapy. However, a clear impact on cancer-specific or overall survival (OS) has not yet been demonstrated for dose-escalated radiotherapy. It is therefore unlikely that a total dose of 70 Gy administered in our patient cohort has a significant negative impact on the cancer-specific and OS.

Differences in the administration of hormonal therapy might also have had a significant impact on outcome. In our cohort, 61.6 % of men received neoadjuvant androgen deprivation and 20.9 % of patients underwent adjuvant hormonal therapy. We therefore included the administration of androgen deprivation as potential confounder in multivariate analyses that showed that plasma fibrinogen levels were independent predictors of survival.

A further limitation might be caused by other potential confounding factors like cardiovascular disease, systemic inflammatory diseases that may independently influence plasma fibrinogen levels. Elderly men and those with comorbid conditions more often undergo radiation therapy compared to younger patients and men without comorbidities. Because of the retrospective design of our study, we were unfortunately unable to apply validated tools for the assessment of comorbidities. There is the possibility that the patients in our cohort might have had concurrent morbidity that could have had a significant impact on OS; however, a major effect of comorbidities on the primary endpoint CSS seems to be unlikely.

In conclusion, although we have found a significant association of an increased plasma fibrinogen level with an impaired CSS and OS, our data have to be interpreted cautiously. Major limitations of our study are caused by its retrospective design and the limited accuracy obtained using ROC curve analysis that was performed to determine the optimal cut-off level for the plasma fibrinogen. Therefore, the present findings have to be regarded as preliminary until validated by additional studies.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study complied with the Declaration of Helsinki and has been approved by the local Ethical Committee.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Palumbo JS (2008) Mechanisms linking tumour cell-associated procoagulant function to tumour dissemination. Semin Thromb Hemost 34:154–160
3. Andreasen PA, Egelund R, Petersen HH (2000) The plasminogen activation system in tumour growth, invasion, and metastasis. Cell Mol Life Sci 57:25–40
4. Brown LF, Van de Water L, Harvey VS, Dvorak HF (1988) Fibrinogen influx and accumulation of cross-linked fibrin in healing wounds and in tumour stroma. Am J Pathol 130:455–465
5. Sahni A, Simpson-Haidaris PJ, Sahni SK, Vaday GG, Francis CW (2008) Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). J Thromb Haemost 6:176–183
6. Wojtukiewicz MZ, Sierko E, Rak J (2004) Contribution of the hemostatic system to angiogenesis in cancer. Semin Thromb Hemost 30:5–20
7. Daly ME, Makris A, Reed M, Lewis CE (2003) Hemostatic regulators of tumour angiogenesis: a source of antiangiogenic agents for cancer treatment? J Natl Cancer Inst 95:1660–1673
8. Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420:860–867
9. Palumbo JS, Kombrinck KW, Drew AF, Grimes TS, Kiser JH, Degen JL, Bugge TH (2000) Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 96:3302–3309
10. Takeuchi H, Ikeuchi S, Kitagawa Y, Shimada A, Oishi T, Isobe Y, Kubochi K, Kitajima M, Matsumoto S (2007) Pretreatment plasma fibrinogen level correlates with tumour progression and metastasis in patients with squamous cell carcinoma of the esophagus. J Gastroenterol Hepatol 22:2222–2227
11. Yamashita H, Kitayama J, Kanno N, Yatomi Y, Nagawa H (2006) Hyperfibrinogenemia is associated with lymphatic as well as hematogenous metastasis and worse clinical outcome in T2 gastric cancer. BMC Cancer 6:147
12. Guo Q, Zhang B, Dong X, Xie Q, Guo E, Huang H, Wu Y (2009) Elevated levels of plasma fibrinogen in patients with pancreatic cancer: possible role of a distant metastasis predictor. Pancreas 38:e75–e79
13. Tang L, Liu K, Wang J, Wang C, Zhao P, Liu J (2010) High preoperative plasma fibrinogen levels are associated with distant metastases and impaired prognosis after curative resection in patients with colorectal cancer. J Surg Oncol 102:428–432
14. Polterauer S, Grimm C, Seebacher V, Concin N, Marth C, Tomovski C, Husslein H, Leipold H, Hefler-Frischmuth K,

Tempfer C, Reinthaller A, Hefler L (2009) Plasma fibrinogen levels and prognosis in patients with ovarian cancer: a multicenter study. Oncologist 14:979–985
15. Polterauer S, Seebacher V, Hefler-Frischmuth K, Grimm C, Heinze G, Tempfer C, Reinthaller A, Hefler L (2009) Fibrinogen plasma levels are an independent prognostic parameter in patients with cervical cancer. Am J Obstet Gynecol 200:647.e1–647.e7
16. Seebacher V, Polterauer S, Grimm C, Husslein H, Leipold H, Hefler-Frischmuth K, Tempfer C, Reinthaller A, Hefler L (2010) The prognostic value of plasma fibrinogen levels in patients with endometrial cancer: a multi-centre trial. Br J Cancer 102:952–956
17. Pichler M, Hutterer GC, Stojakovic T, Mannweiler S, Pummer K, Zigeuner R (2013) High plasma fibrinogen level represents an independent negative prognostic factor regarding cancer-specific, metastasis-free, as well as overall survival in a European cohort of non-metastatic renal cell carcinoma patients. Br J Cancer 109:1123–1129. doi:10.1038/bjc.2013.443
18. Pichler M, Dalpiaz O, Ehrlich GC, Stojakovic T, Martín Hernández JM, Mannweiler S, Pummer K, Zigeuner R, Hutterer GC (2013) Validation of the preoperative plasma fibrinogen level as a prognostic factor in a European cohort of patients with localized upper tract urothelial carcinoma. J Urol 191:920–925. doi:10.1016/j.juro.2013.10.073
19. Zheng S, Shen J, Jiao Y, Liu Y, Zhang C, Wei M, Hao S, Zeng X (2009) Platelets and fibrinogen facilitate each other in protecting tumour cells from natural killer cytotoxicity. Cancer Sci 100:859–865
20. Steinbrecher KA, Horowitz NA, Blevins EA, Barney KA, Shaw MA, Harmel-Laws E, Finkelman FD, Flick MJ, Pinkerton MD, Talmage KE, Kombrinck KW, Witte DP, Palumbo JS (2010) Colitis-associated cancer is dependent on the interplay between the hemostatic and inflammatory systems and supported by integrin alpha(M)beta(2) engagement of fibrinogen. Cancer Res 70:2634–2643. doi:10.1158/0008-5472.CAN-09-3465
21. Ziaran S, Goncalves FM, Breza J Sr (2013) Patients with prostate cancer treated by ADT have significantly higher fibrinogenemia than healthy control. World J Urol 31:289–292. doi:10.1007/s00345-012-0926-x
22. Seal US, Doe RP, Byar DP, Corle DK (1976) Response of plasma fibrinogen and plasminogen to hormone treatment and the relation of pretreatment values to mortality in patients with prostatic cancer. Cancer 38:1108–1117
23. McDonald AC, Vira MA, Vidal AC, Gan W, Freedland SJ, Taioli E (2014) Association between systemic inflammatory markers and serum prostate-specific antigen in men without prostatic disease—the 2001–2008 National Health and Nutrition Examination Survey. Prostate 74:561–567. doi:10.1002/pros.22782
24. Tiedje V, Dunkler D, Ay C, Horvath B, Quehenberger P, Pabinger M, Zielinski C, Pabinger I, Mannhalter C (2011) The role of fibrinogen plasma levels, the -455G>A fibrinogen and the factor XIII A subunit (FXIII-A) Val34Leu polymorphism in cancer-associated venous thrombosis. Thromb Haemost 106:908–913. doi:10.1160/TH11-04-0278
25. Song SW, Lee HS, Kim MS, Lee JM, Kim JH, Nam BH, Zo JI (2006) Preoperative serum fibrinogen level predicts postoperative pulmonary complications after lung cancer resection. Ann Thorac Surg 81:1974–1981