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ORIGINAL SCIENTIFIC REPORT

Usefulness of Preoperative Plasma Fibrinogen Versus Other Prognostic Markers for Predicting Gastric Cancer Recurrence

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Abstract

Background Hypercoagulation is associated with tumor progression and metastasis in various types of malignancy. We compared the prognostic value of preoperative plasma fibrinogen level with those of other prognostic markers in patients with gastric cancer and assessed whether fibrinogen level was an independent prognostic indicator.

Methods We collected preoperative data from 609 consecutive patients with gastric cancer who underwent curative gastrectomy. A receiver operating curve (ROC) was used to compare the sensitivity and specificity of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), C-reactive protein (CRP), platelet count, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and fibrinogen level in predicting recurrence. Recurrence-free survival (RFS) and overall survival (OS) were compared between the normal and high fibrinogen groups.

Results In the ROC analysis, the area under the curve (AUC) was 0.534 for CEA, 0.552 for CA19-9, 0.587 for CRP, 0.565 for platelet count, 0.567 for PLR, 0.522 for NLR, and 0.692 for fibrinogen. Plasma fibrinogen level increased with tumor stage. The high fibrinogen (≥350 mg/dl) group had significantly worse RFS ($p < 0.001$) and OS ($p < 0.001$) than the normal fibrinogen (<350 mg/dl) group. Cox multivariate analysis of RFS revealed that fibrinogen level was an independent prognostic factor ($p < 0.001$) in addition to sex, pT stage, and pN stage.

Conclusions Preoperative plasma fibrinogen level had the highest predictive value for recurrence among seven known prognostic markers. Since fibrinogen level is an independent factor for RFS, it would be useful for predicting prognosis after gastric cancer surgery.

Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer death worldwide [1–3]. Although surgery is the only curative treatment for gastric cancer, the high recurrence rate after surgery has not substantially improved. Many studies have shown that various prognostic markers based on blood tests can predict recurrence after surgery in patients with gastric cancer. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are commonly used tumor markers, but they have insufficient sensitivity and specificity for detecting recurrence in patients with gastric cancer [4, 5]. However, there are other prognostic markers based on blood tests. A previous study reported that C-reactive protein (CRP) was associated with tumor stage and might be predictive of tumor invasion and lymph node metastasis in patients with gastric cancer [6]. With regards to platelet count, thrombocytosis and platelet-to-lymphocyte ratio (PLR) have been reported as independent prognostic

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markers in patients with gastric cancer [7, 8]. Neutrophil-to-lymphocyte ratio (NLR) reflects inflammation status and is associated with clinical stage and survival in patients with gastric cancer [9].

In addition, some studies have focused on the relationship between various cancers and hemostasis [10, 11]. Hypercoagulation, as indicated by high fibrinogen level, has been reported to be associated with tumor progression, metastasis, and survival in patients with gastric cancer [12, 13]. However, there have not been any studies comparing the prognostic value of fibrinogen and other prognostic markers. Thus, the aim of this study was to compare the sensitivity and specificity of preoperative plasma fibrinogen to those of other prognostic markers, such as CEA, CA19-9, CRP, platelet count, PLR, and NLR, for predicting recurrence in patients with gastric cancer. We also assessed whether fibrinogen is an independent prognostic indicator after adjusting for other prognostic factors in a multivariate analysis.

Patients and methods

Patients

We reviewed the records of 949 consecutive patients who underwent gastrectomy for histologically diagnosed adenocarcinoma of the stomach between January 2001 and December 2011 at Osaka University Hospital. Patients who underwent R1 or R2 resection, received neoadjuvant chemotherapy before surgery, or died within 30 days of surgery were excluded. Pathological tumor stage was evaluated using the third English edition of the Japanese classification of gastric carcinoma, which was established by Japanese Gastric Cancer Association [14]. Levels of plasma fibrinogen, serum CEA, serum CA19-9, serum CRP, as well as platelet, lymphocyte, and neutrophil counts, were examined within 30 days before surgery. The cut-off value for fibrinogen was defined as 350 mg/dl, based on the upper reference value at our hospital and other report [15]. This study was approved by the institutional review board of Osaka University Hospital.

Statistical analysis

A receiver operating curve (ROC) was used to compare the sensitivity and specificity of fibrinogen levels for predicting recurrence compared to those of other biomarkers. Associations between fibrinogen and clinicopathological factors were analyzed using the Chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables. Recurrence-free survival (RFS) was defined as the period from the date of surgery to the date of detection of the first recurrence or death from any cause. Overall survival (OS) was defined as the period from the date of surgery to the date of death from any cause. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. The hazard ratio (HR) for recurrence or death in the high fibrinogen group was estimated with a Cox proportional hazards model. Multivariate Cox regression analysis was performed to adjust for potential confounding factors. A statistically significant difference was indicated by $p < 0.05$. All statistical analyses were performed using SPSS Statistics software, version 22 (IBM Corp., Armonk, NY, USA).

Results

This study included 609 eligible patients with data available for seven variables: CEA, CA19-9, CRP, platelet count, PLR, NLR, and fibrinogen. The ROC for predicting recurrence is shown in Fig. 1. The area under the curve (AUC) was 0.534 for CEA, 0.552 for CA19-9, 0.587 for CRP, 0.565 for platelet count, 0.567 for PLR, 0.522 for NLR, and 0.692 for fibrinogen. When the cut-off value for fibrinogen was defined as 350 mg/dl, the upper reference value at our hospital, the sensitivity and specificity of fibrinogen were 52 and 78 %, respectively.

We examined the association between fibrinogen and clinicopathological factors (Table 1). The normal fibrinogen (<350 mg/dl) group included 445 patients (73.1 %),

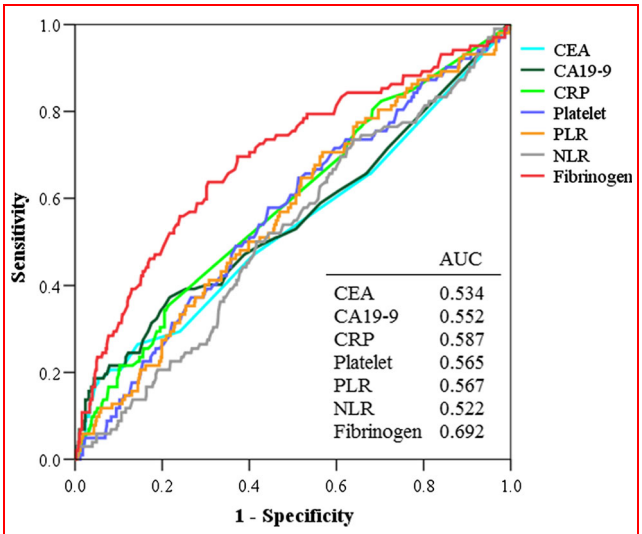

Fig. 1 Receiver operating curve (ROC) for predicting recurrence with carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), C-reactive protein (CRP), platelet count, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), or fibrinogen

Table 1 Baseline characteristics of 609 patients between the normal and high fibrinogen groups

Characteristics	Normal fibrinogen (<350 mg/dl) group ($n = 445$)	High fibrinogen (≥350 mg/dl) group ($n = 164$)	p value
Age (years)			0.005
Median (range)	66 (30–92)	68 (37–86)	
Sex			0.600
Male	316 (71.0 %)	120 (73.2 %)	
Female	129 (29.0 %)	44 (26.8 %)	
Location			0.071
Upper	112 (25.2 %)	56 (34.1 %)	
Middle	173 (38.9 %)	52 (31.7 %)	
Lower	160 (36.0 %)	56 (34.1 %)	
Histological type			0.303
Differentiated	238 (53.5 %)	80 (48.8 %)	
Undifferentiated	207 (46.5 %)	84 (51.2 %)	
pT			<0.001
T1	273 (61.3 %)	61 (37.2 %)	
T2	58 (13.0 %)	24 (14.6 %)	
T3	80 (18.0 %)	40 (24.4 %)	
T4	34 (7.6 %)	39 (23.8 %)	
pN			0.013
N0	318 (71.5 %)	96 (58.5 %)	
N1	52 (11.7 %)	27 (16.5 %)	
N2	45 (10.1 %)	20 (12.2 %)	
N3	30 (6.7 %)	21 (12.8 %)	
pStage			<0.001
I	288 (64.7 %)	70 (42.7 %)	
II	89 (20.0 %)	48 (29.3 %)	
III	66 (14.8 %)	42 (25.6 %)	
IV	2 (0.4 %)	4 (2.4 %)	
Adjuvant chemotherapy			0.005
Yes	74 (16.6 %)	44 (26.8 %)	
No	371 (83.4 %)	120 (73.2 %)	

and the high fibrinogen (≥350 mg/dl) group had 164 patients (26.9 %). The high fibrinogen group included more patients of older age ($p = 0.005$), advanced pT stage ($p < 0.001$), and advanced pN stage ($p = 0.013$). Sex, tumor location, and histological type were not significantly associated with fibrinogen levels. Plasma fibrinogen levels increased with tumor stage (Fig. 2).

The median follow-up time for all patients in this study was 55 months. When all patients were grouped into quartiles by plasma fibrinogen level, there was a difference in RFS among the quartiles (log-rank $p < 0.001$), but the lowest and second lowest quartiles had similar RFS (Fig. 3a). Based on the cut-off value of 350 mg/dl, the high

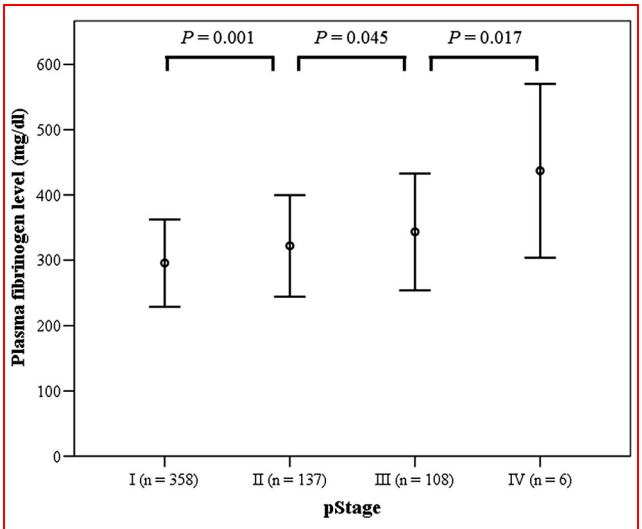

Fig. 2 Mean and standard deviation of plasma fibrinogen levels by pathological tumor stage. p values were calculated with t test

fibrinogen group had significantly worse RFS than the normal fibrinogen group [HR 3.42; 95 % confidence interval (CI) 2.38–4.91; log-rank $p < 0.001$] (Fig. 3b). The 5-year RFS rate in the high fibrinogen group was 62.0 %, compared to 86.1 % in the normal fibrinogen group. The high fibrinogen group had also significantly worse OS than the normal fibrinogen group [HR 2.73; 95 % CI 1.80–4.14; log-rank $p < 0.001$]. The 5-year OS rate was 73.2 % in the high fibrinogen group and 89.3 % in the normal fibrinogen group. Recurrence was observed in 102 patients (normal fibrinogen group, 49 patients; high fibrinogen group, 53 patients). Regarding the first site of recurrence, the high fibrinogen group had significantly more common recurrence in the peritoneum ($p = 0.008$), liver ($p < 0.001$), and lymph nodes ($p < 0.001$) than the normal fibrinogen group (Table 2).

Subgroup analysis by pT stage showed that the high fibrinogen group had significantly worse RFS than the normal fibrinogen group in both the pT1–2 (log-rank $p < 0.001$) and pT3–4 subgroups (log-rank $p = 0.003$) (Fig. 4a, b). There was also a significant difference in the pT1–2 (log-rank $p = 0.003$) and pT3–4 subgroups (log-rank $p = 0.017$) with regards to OS. Even when we divided patients into pT1 and pT2–4 subgroups, both subgroups showed significant differences between the normal and high fibrinogen groups (pT1, log-rank $p = 0.050$; pT2–4, $p < 0.001$). We also conducted another subgroup analysis of RFS by the presence or absence of adjuvant chemotherapy. The analysis showed that the high fibrinogen group had significantly worse RFS than the normal fibrinogen group in both subgroups (with adjuvant chemotherapy, log-rank $p = 0.004$; without adjuvant chemotherapy, log-rank $p < 0.001$).

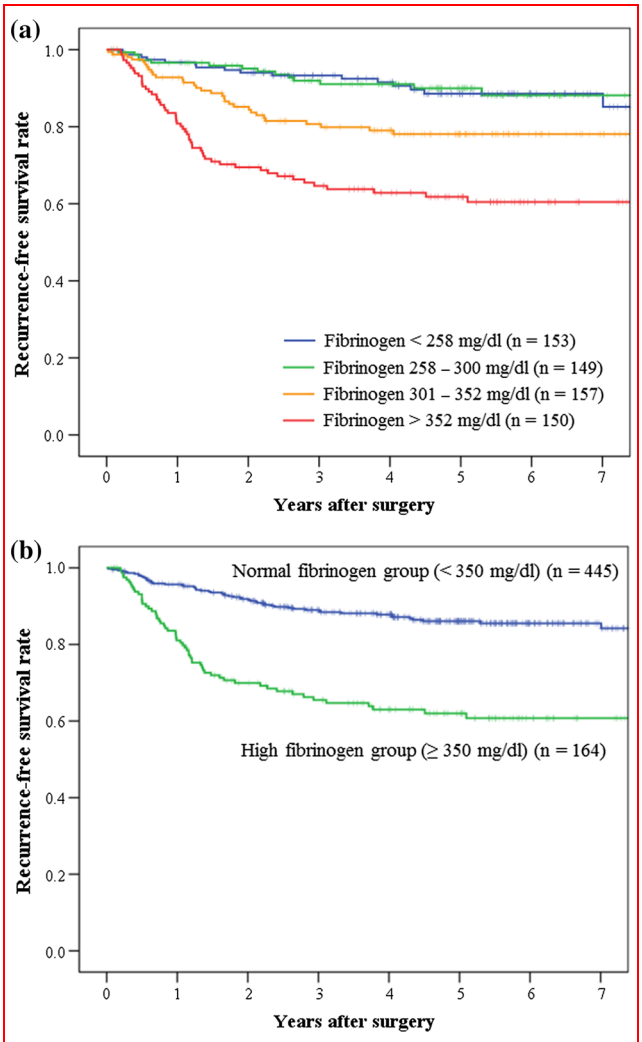

Fig. 3 Recurrence-free survival by plasma fibrinogen level quartile (**a**) and between the normal and high fibrinogen groups (**b**)

Cox multivariate analysis of fibrinogen and seven clinicopathological factors (age, sex, tumor location, histological type, pT stage, pN stage, and adjuvant chemotherapy) revealed that fibrinogen ≥350 mg/dl was a statistically significant independent prognostic factor of poor RFS, along with male sex, pT3–4 disease, and pN1–3 disease (Table 3). The adjusted HR for recurrence in the high fibrinogen group was 2.25 (95 % CI 1.55–3.28; $p < 0.001$). Even when operative procedure (total gastrectomy or other), surgical approach (open or laparoscopic), and lymphadenectomy (D2 or other) were included in the Cox multivariate analysis as intermediate factors, the HR for recurrence in the high fibrinogen group was not essentially changed (HR 2.21; 95 % CI 1.51–3.22; $p < 0.001$).

Discussion

There have been many studies focused on predicting prognosis using preoperative blood tests in patients with gastric cancer. Although some studies have identified CEA, CA19-9, CRP, platelet count, PLR, and NLR as prognostic markers in patients with gastric cancer, there have been no studies evaluating which markers are best suited to predict recurrence in gastric cancer [4–9, 12, 13]. Based on ROC analysis, this study revealed that preoperative plasma fibrinogen level had the highest prognostic value compared with other six preoperative markers in patients with gastric cancer. The high fibrinogen group was significantly older, had more advanced pT and pN stage, and was an independent factor for poor RFS.

Cancer patients are often in a hypercoagulable state [16]. Some studies have shown that cancer patients have higher fibrinogen levels than non-cancer patients [11, 17]. Previous studies have described the mechanisms of hyperfibrinogenemia in patients with malignancy [13, 18–21]. Malignant cells often have high levels of the fibrinogen receptor called intercellular adhesion molecule 1 (ICAM-1), and platelets also have a fibrinogen receptor called αIIβ3 integrin. As a result, malignant cells bind to platelets through fibrinogen. These aggregates form tumor thrombi that bind to the endothelium of other organs. Through this mechanism, fibrinogen plays a role in tumor progression and metastasis.

Table 2 First sites of recurrence between the normal and high fibrinogen groups

	Normal fibrinogen (<350 mg/dl) group ($n = 445$)	High fibrinogen (≥350 mg/dl) group ($n = 164$)	p value
Total	49 (11.0 %)	53 (32.3 %)	<0.001
Peritoneum	26 (5.8 %)	20 (12.2 %)	0.008
Liver	9 (2.0 %)	18 (11.0 %)	<0.001
Lymph nodes	8 (1.8 %)	14 (8.5 %)	<0.001
Others	6 (1.3 %)	9 (5.5 %)	0.003

High fibrinogen group included eight duplicated cases

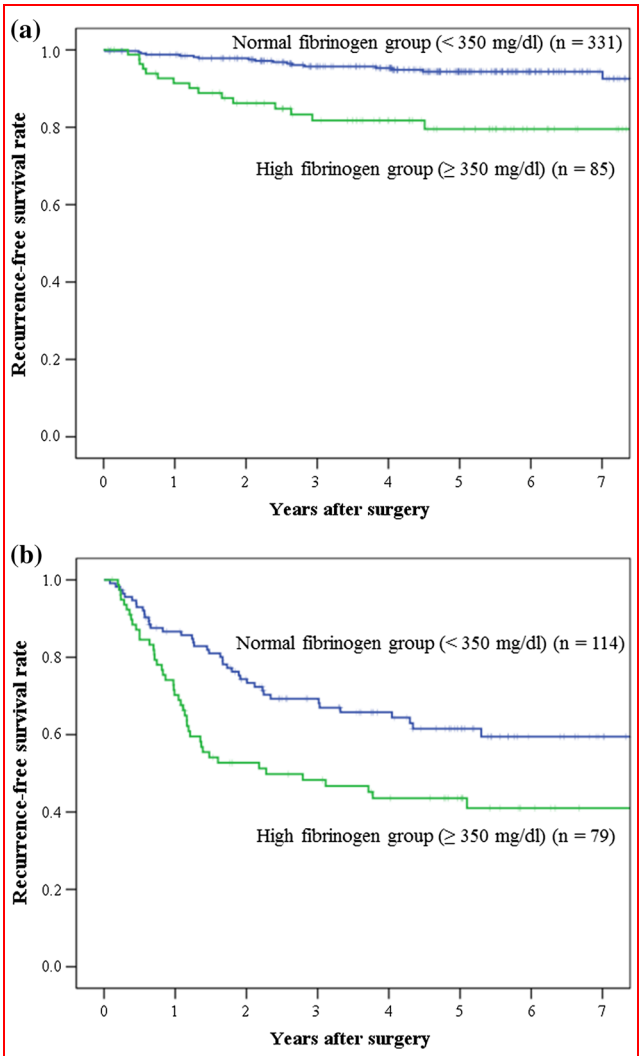

Fig. 4 Recurrence-free survival of patients with pT1–2 (**a**) and pT3–4 tumors (**b**) between the normal and high fibrinogen groups

Previous studies have shown that preoperative fibrinogen level in patients with gastric cancer is associated with tumor progression and metastasis [11–13, 22]. Yamashita et al. reported that the OS rate in patients with T2 tumors was significantly lower in the high fibrinogen group than that in the normal fibrinogen group, but there was no difference in the two groups among patients with T3–4 tumors [13]. They speculated that high preoperative fibrinogen levels reflected only lymph node or liver metastases but not peritoneal metastasis, but our study suggests that fibrinogen levels can be statistically associated with any type of recurrence, including peritoneal metastasis. Indeed, there have been some studies suggesting that fibrinogen might play a crucial role in the development of peritoneal carcinomatosis [23, 24]. As a result of the increased permeability of tumor microvessels, plasma fibrinogen can extravasate into the peritoneal cavity and accumulate in the peritoneum, where it is degraded to fibrin by thrombin. In the peritoneum, fibrin may help stimulate neovascularization and provide the matrix that reorganizes the stroma, thereby enhancing tumor metastasis to the abdominal cavity. Thus, this mechanism is consistent with our findings. However, adjuvant chemotherapy may decrease the peritoneal recurrence even in the high fibrinogen patients. Indeed, there were no significant difference between peritoneal recurrence and fibrinogen level in the patients who underwent adjuvant chemotherapy in our study (log-rank $p = 0.752$).

There are some limitations in this study. Our study included some censored cases who did not reach 5 years after surgery, which may indicate the possibility of bias in the survival analyses. Another limitation was retrospective and single-institution study, which may lead to some potential biases. Thus, a prospective multicenter study to validate our findings is warranted.

In conclusion, we revealed that preoperative plasma fibrinogen levels have the highest value for predicting recurrence among seven known prognostic markers in patients with gastric cancer. Predicting recurrence and prognosis in patients with gastric cancer using preoperative fibrinogen levels in addition to TNM stage may help determine whether adjuvant chemotherapy is indicated.

Table 3 Cox multivariate analysis for recurrence-free survival

Variables	Categories	HR (95 % CI)	*p* value
Age (years)	>65	1.37 (0.94–2.00)	0.101
Sex	Male	1.83 (1.17–2.87)	0.008
Location	Upper	1.27 (0.87–1.86)	0.215
Histological type	Undifferentiated	1.06 (0.72–1.56)	0.755
pT	T3–4	3.95 (2.51–6.22)	<0.001
pN	N1–3	3.31 (2.15–5.08)	<0.001
Adjuvant chemotherapy	No	1.08 (0.71–1.65)	0.712
Fibrinogen level	≥350 mg/dl	2.25 (1.55–3.28)	<0.001

HR hazard ratio, *CI* confidence interval

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Compliance with ethical standards

Conflict of Interest There is no conflict of interest regarding the manuscript.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5):E359–E386
2. Shinohara S, Korenaga D, Edagawa A et al (2013) Significant prognostic factors in patients with Stage IV gastric cancer with special reference to the curability of surgery. Surg Today 43(1):40–47
3. Yoshikawa T, Rino Y, Yukawa N et al (2014) Neoadjuvant chemotherapy for gastric cancer in Japan: a standing position by comparing with adjuvant chemotherapy. Surg Today 44(1): 11–21
4. Kochi M, Fujii M, Kanamori N et al (2000) Evaluation of serum CEA and CA19-9 levels as prognostic factors in patients with gastric cancer. Gastric Cancer 3(4):177–186
5. Huang ZB, Zhou X, Xu J et al (2014) Prognostic value of preoperative serum tumor markers in gastric cancer. World J Clin Oncol 5(2):170–176
6. Kim DK, Oh SY, Kwon HC et al (2009) Clinical significances of preoperative serum interleukin-6 and C-reactive protein level in operable gastric cancer. BMC Cancer 9:155
7. Ikeda M, Furukawa H, Imamura H et al (2002) Poor prognosis associated with thrombocytosis in patients with gastric cancer. Ann Surg Oncol 9(3):287–291
8. Zhou X, Du Y, Huang Z et al (2014) Prognostic value of PLR in various cancers: a meta-analysis. PLoS One 9(6):e101119
9. Shimada H, Takiguchi N, Kainuma O et al (2010) High preoperative neutrophil-lymphocyte ratio predicts poor survival in patients with gastric cancer. Gastric Cancer 13(3):170–176
10. Trousseau A (1965) Phlegmasia alba dolens. In: Clinique Medicale de L'Hotel Dieu de Paris, 2nd edition. Balliere, p 654–656
11. Di Micco P, Romano M, Niglio A et al (2001) Alteration of haemostasis in non-metastatic gastric cancer. Dig Liver Dis 33(7):546–550
12. Yamashita H, Kitayama J, Nagawa H (2005) Hyperfibrinogenemia is a useful predictor for lymphatic metastasis in human gastric cancer. Jpn J Clin Oncol 35(10):595–600
13. Yamashita H, Kitayama J, Kanno N et al (2006) Hyperfibrinogenemia is associated with lymphatic as well as hematogenous metastasis and worse clinical outcome in T2 gastric cancer. BMC Cancer 6:147
14. Sano T, Aiko T (2011) New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. Gastric Cancer 14(2):97–100
15. Takeuchi H, Ikeuchi S, Kitagawa Y et al (2007) Pretreatment plasma fibrinogen level correlates with tumor progression and metastasis in patients with squamous cell carcinoma of the esophagus. J Gastroenterol Hepatol 22(12):2222–2227
16. Dvorak HF (1987) Thrombosis and cancer. Hum Pathol 18(3):275–284
17. Modrau II, Iversen LL, Thoriacius-Ussing OO (2001) Hemostatic alterations in patients with benign and malignant colorectal disease during major abdominal surgery. Thromb Res 104(5): 309–315
18. Bennett JS, Hoxie JA, Leitman SF et al (1983) Inhibition of fibrinogen binding to stimulated human platelets by a monoclonal antibody. Proc Natl Acad Sci USA 80(9):2417–2421
19. Honn KV, Tang DG, Crissman JD (1992) Platelets and cancer metastasis: a causal relationship? Cancer Metastasis Rev 11(3–4):325–351
20. Languino LR, Plescia J, Duperray A et al (1993) Fibrinogen mediates leukocyte adhesion to vascular endothelium through an ICAM-I -dependent pathway. Cell 73(7):1423–1434
21. Biggerstaff JP, Seth N, Amirkhosravi A et al (1999) Soluble fibrin augments platelet/tumor cell adherence in vitro and in vivo, and enhances experimental metastasis. Clin Exp Metastasis 17(8):723–730
22. Lee SE, Lee JH, Ryu KW et al (2012) Preoperative plasma fibrinogen level is a useful predictor of adjacent organ involvement in patients with advanced gastric cancer. J Gastric Cancer 12(2):81–87
23. Nagy JA, Meyers MS, Msse EM et al (1995) Pathogenesis of ascites tumor growth: fibrinogen influx and fibrin accumulation in tissues lining the peritoneal cavity. Cancer Res 55(2):369–375
24. Ma Y, Qian Y, Lv W (2007) The correlation between plasma fibrinogen levels and the clinical features of patients with ovarian carcinoma. J Int Med Res 35(5):678–684