RESEARCH ARTICLE

Preoperative Thrombocytosis and Poor Prognostic Factors in Endometrial Cancer

Suttichai Heng, Mongkol Benjapibal*

Abstract

This study aimed to evaluate the prevalence of preoperative thrombocytosis and its prognostic significance in Thai patients with endometrial cancer. We retrospectively reviewed the medical records of 238 cases who had undergone surgical staging procedures between January 2005 and December 2008. Associations between clinicopathological variables and preoperative platelet counts were analyzed using Pearson's chi square or two-tailed Fisher's exact tests. Survival analysis was performed with Kaplan-Meier estimates. Univariate and Cox-regression models were used to evaluate the prognostic impact of various factors including platelet count in terms of disease-free survival and overall survival. The mean preoperative platelet count was 315,437/μL (SD 100,167/μL). Patients who had advanced stage, adnexal involvement, lymph node metastasis, and positive peritoneal cytology had significantly higher mean preoperative platelet counts when compared with those who had not. We found thrombocytosis (platelet count greater than 400,000/μL) in 18.1% of our patients with endometrial cancer. These had significant higher rates of advanced stage, cervical involvement, adnexal involvement, positive peritoneal cytology, and lymph node involvement than patients with a normal pretreatment platelet count. The 5-year disease-free survival and overall survival were significantly lower in patients who had thrombocytosis compared with those who had not (67.4% *vs.* 85.1%, p=0.001 and 86.0% *vs.* 94.9%, p=0.034, respectively). Thrombocytosis was shown to be a prognostic factor in the univariate but not the multivariate analysis. In conclusion, presence of thrombocytosis is not uncommon in endometrial cancer and may reflect unfavorable prognostic factors but its prognostic impact on survival needs to be clarified in further studies.

Keywords: Platelet count - thrombocytosis - prognostic factors - endometrial cancer

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Introduction

Haemostatic abnormalities are frequently observed in patients with malignancy. Most patients with cancer have evidence of subclinical activation of blood coagulation. Clinically, cancer patients with advanced disease are characterized by a variety of venous thromboembolic disorders. The mechanistic framework that helps to understand and group the causes of thromboembolism is an extension of the triad of Virchow, which postulates that thrombosis is caused by changes in blood flow, the state of the vessel wall, and/or the composition of blood. Platelets have historically been ignored in studies of VTE. Several lines of research indicate though that platelets play a determining role nowadays. Common and well-established risk factors and presumed points of action of malignancy that cause thromboembolism were microparticles, innate immunity and platelet numbers (Pieter et al., 2012). The association between elevated platelets counts and malignancies was recognized over a century ago (Riess, 1872). Thrombocytosis (generally defined as platelet count greater than 400000/μL) has been demonstrated in a variety of solid tumors, such as lung, kidney, breast, esophagus, gastric, and colon cancers (Pedersen and Milman, 1996; Monreal et al., 1998; Ikeda et al., 2002; Taucher et al., 2003; Shimada et al., 2004; Erdemir et al., 2007). The prevalence of thrombocytosis varies widely, ranging from 10% to 57% of patients with cancer (Sierko and Wojtukiewicz, 2004). The pathogenesis of thrombocytosis in malignancy has not yet been clarified. However, there have been evidences that the tumor cells secrete humoral factors which may eventually lead to thrombocytosis (Nakazaki, 1992; Lidor et al., 1993; Kabir and Darr, 1995; Wu et al., 1996). Preoperative thrombocytosis has also been observed and found to be a poor prognostic variable in gynecological malignancies including vulvar, cervical, ovarian, and endometrial cancers (Hernandez et al., 1992; Zeimet et al., 1994; Menczer et al., 1996; Gucer et al., 1998; Hefler et al., 2000; Hernandez et al., 2000; Scholz et al., 2000; Tamussino et al., 2001; Li et al., 2004; Ayhan et al., 2006; Metindir and Dilek, 2009).

Endometrial cancer is the most common cancer of the female genital tract in developed countries. Abnormal

Affiliations: Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
**For correspondence: mongkol.ben@mahidol.ac.th*

vaginal bleeding, especially in postmenopause, is the most common presenting symptom in patients with endometrial cancer and the majority of cases are diagnosed while the disease is confined in the uterine corpus. In Thailand, it is the third most common gynecological malignancy after cervical and ovarian cancer with an annual incidence of 4.3 per 100,000 women, and an annual death rate of 1.1 per 100,000 women per year (Ferlay et al., 2010). Only few data are currently available concerning the association between thrombocytosis and prognostic factors in endometrial cancer (Menczer et al., 1996; Gucer et al., 1998; Scholz et al., 2000; Tamussino et al., 2001; Ayhan et al., 2006; Metindir and Dilek, 2009). To the best of our knowledge, there are no reports investigating such a relationship in Thailand. The objective of our study was to determine the prevalence and prognostic value of preoperative thrombocytosis in Thai women with endometrial cancer.

Materials and Methods

The hospital records of patients with histologically confirmed endometrial cancer who underwent primary surgical staging procedure at the Department of Obstetrics and Gynecology, Siriraj Hospital were reviewed. Surgical staging procedure consisted of total hysterectomy with bilateral salpingo-oophorectomy with selective pelvic and paraaortic lymph node dissection. Peritoneal washing for cytology was optional. Criteria for selective pelvic and paraaortic lymph node dissection were tumor size larger than 2 cm in greatest diameter, high grade endometrioid carcinoma (grade 2 or 3), deep myometrial invasion (>50% of myometrial thickness), or some specific histology (serous or clear cell). The tumor stage and histological diagnosis of each case were surgically determined according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO staging system, 2009) and the histological classification of the World Health Organization (WHO), respectively. Endometrioid tumors were graded as well (G1), moderately (G2), or poorly (G3) differentiated. Adjuvantly, patients with high grade tumor, serous or clear cell histology, deep myometrial invasion, cervical extension, adnexal involvement, positive peritoneal cytology, and lymph node metastasis received radiotherapy, or chemotherapy, or both. Patients without these histological factors received no adjuvant treatment. Patients with missing preoperative platelet counts, having concurrent other malignancy or conditions associated with thrombocytosis (i.e., collagen vascular disease, secondary malignancies, and chronic obstructive pulmonary disease) were excluded from the analysis.

Blood platelet count in each patient was obtained within 2 weeks prior to the surgery. Thrombocytosis was defined as platelet count of greater than 400000/μL consistent with prior reports in the literature (Costantini et al., 1990; Zeimet et al., 1994; Pedersen and Milman, 1996; Gucer et al., 1998; O'Keefe et al., 2002; Gorelick et al., 2009). Data were analyzed using χ^2 test, student t-test and Fisher exact test as appropriated. Association between clinicopathological variables (histology, grading, stage, myometrial invasion, lymphovascular space invasion, cervical involvement, adnexal involvement, peritoneal cytology, and lymph node status) and preoperative platelet counts were described using Pearson's chi square test (or two-tailed Fisher's exact test wnen appropriate). Survival analysis was performed with Kaplan-Meier estimates. Univariate and Cox-regression models were used to evaluate the prognostic impact of various factors including platelet count in terms of disease-free survival and overall survival. Data management and statistics were analyzed using PASW statistics 18.0 (IBM Corporation, New York, NY, USA). A p-value of <0.05 was taken for statistical significance. The research project was approved by the ethical committee of the Siriraj Hospital, Mahidol University, and was conducted in accordance with the Declaration of Helsinki.

Results

Between January 2005 and December 2008, 251 patients with endometrial cancer underwent surgical staging at the Department of Obstetrics and Gynecology, Siriraj Hospital. Thirteen patients were excluded from the study because of missing pretreatment platelet counts, having concurrent other malignancy and conditions associated with thrombocytosis, so the remaining 238 patients were qualified for the final analysis. The age range of the patients was 28-88 years with a mean age of 57.88+10.03 years. Histologically, while 196 (82.4%) patients were endometrioid, the remaining 42 (17.6%) had non-endometrioid histology. Tumor grade among 196 patients with endometrioid histology was G1 in 109 (55.6%) patients, G2 in 65 (33.2%), and G3 in 22 (11.2%). Stage of the disease was early in the majority of the patients (68.9% stage 1, 9.2% stage 2). Approximately one third of the patients had deep myometrial invasion. Thirty-nine (17.2%) of the 227 patiens was found to have lymphovascular space invasion. Cervical and adnexal involvement was observed in 44 (18.5%) and 29 (12.2%) patients, respectively. Twenty-two (10.9%) of the 201 patients had positive peritoneal cytology. Among 198 patients who underwent lymphadenectomy, 23 (11.6%) had nodal involvement, and the remaining did not. Ninety-five patients (39.9%) received radiation only, 25 (10.5%) received chemotherapy only, 10 (4.2%) received both radiation and chemotherapy, and 108 (45.4%) received no adjuvant treatment. The median duration of follow-up was 59.6 months (range, 1.0-98.0 months) and median overall survival was not reached. The 5-year disease-free survival and overall survival probability were 81.9% and 93.3%, respectively. At the end of the observation period, 193 patients (81.1%) were tumor free, 28 patients (11.8%) were alive with tumor, 15 patients (6.3%) had died of their disease and 2 patients (0.8%) had died from non-cancer related conditions.

Overall mean preoperative platelet count was 315437/μL (SD 100167/μL). Patients who had advanced stage, adnexal involvement, lymph node metastasis, and positive peritoneal cytology had significantly higher mean preoperative platelet counts when compared with those who had not (Table 1). One hundred and ninety-five patients (81.9%) of patients had a preoperative

platelet count lower than 400000μL, while the remaining 43 (18.1%) exhibited preoperative thrombocytosis. Correlation between thrombocytosis and baseline patients' characteristics are given in Table 2. These 43 patients with thrombocytosis had significant higher rates of advanced FIGO stage, cervical involvement, adnexal involvement, positive peritoneal cytology, and lymph node involvement than patients with normal pretreatment platelet count (<400000/μL). The 5-year disease-free survival and overall survival were significantly lower in patients with thrombocytosis compared with those with normal platelet count (67.4% *vs*. 85.1%, p=0.001 and 86.0% *vs*. 94.9%, p=0.034, respectively) (Figure 1,2). Univariate and multivariate analysis to demonstrate the prognostic influence of all variables in term of 5-year disease-free survival and overall survival are shown in Tables 3 and

Table 1. Clinicopathological Parameters in Relation to Mean Platelet Count

	n	Mean platelet count (/μL)	p-value
Histologic type			
Endometrioid	196	314388	0.365
Non-endometrioid	42	320333	
Tumor grade (n=196)			
1	109	301239	0.121
2-3	87	330862	
FIGO stage			
I-II	186	303581	0.003
III-IV	52	357846	
Myometrial invasion			
<1/2	162	308031	0.433
>1/2	76	331224	
Cervical involvement			
Yes	44	338159	0.18
No	194	310284	
Adnexal involvement			
Yes	29	395724	<0.001
No	209	304297	
lymphovascular space invasion (n = 227)			
Yes	39	335795	0.148
No	188	311335	
Peritoneal cytology (n = 201)			
Positive	22	362955	0.001
Negative	179	306765	
Lymph node metastasis (n = 198)			
Yes	23	372478	0.008
No	175	303366	

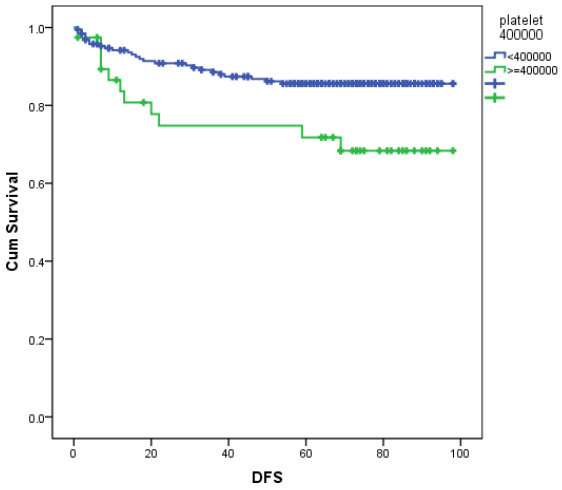

Figure 1. Disease-Free Interval

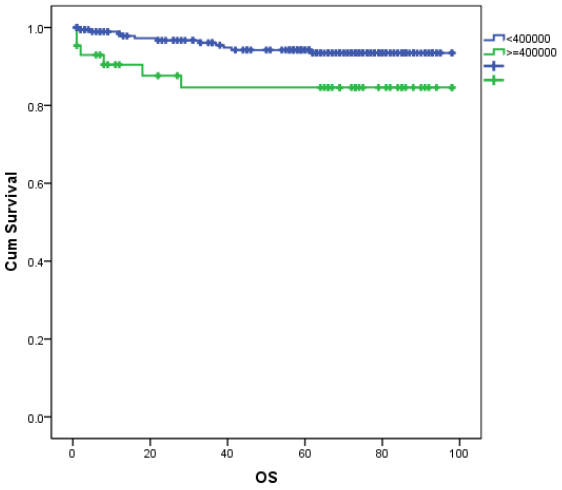

Figure 2. Overall Survival

Table 2. Association of Clinicopathological Parameters and Thrombocytosis

Clinicopathological characteristics	n		Preoperative platelet count: Normal platelet count (<400000/μL) n=195	Thrombocytosis (>400000/μL) n=43	p-value
Histologic type	Endometrioid	196	162 (83.1%)	34 (79.1%)	0.533
	Non-endometrioid	42	33 (16.9%)	9 (20.9%)	
Tumor grade (n=196)	1	109	93 (57.4%)	16 (47.1%)	0.083
	2-3	87	69 (42.6%)	18 (52.9%)	
FIGO stage	I-II	186	160 (82.1%)	26 (60.5%)	0.002
	III-IV	52	35 (17.9%)	17 (39.5%)	
Myometrial invasion	<1/2	162	136 (69.7%)	26 (60.5%)	0.237
	>1/2	76	59 (30.3%)	17 (39.5%)	
Cervical involvement	Yes	44	31 (15.9%)	13 (30.2%)	0.028
	No	194	164 (84.1%)	30 (69.8%)	
Adnexal involvement	Yes	29	15 (7.7%)	14 (32.6%)	<0.001
	No	209	180 (92.3%)	29 (67.4%)	
lymphovascular space invasion (n = 227)	Yes	39	31 (16.7%)	8 (19.5%)	0.662
	No	188	155 (83.3%)	33 (80.5%)	
Peritoneal cytology (n = 201)	Positive	22	15 (8.9%)	7 (21.2%)	0.039
	Negative	179	153 (90.1%)	26 (78.8%)	
Lymph node metastasis (n = 198)	Yes	23	14 (8.4%)	9 (28.1%)	0.001
	No	175	152 (91.6%)	23 (71.9%)	

Table 3. Multivariate Analysis for Disease-Free Survival

	Crude HR	p-value	Adjusted HR	p-value
Older age (>50 years)	1.42 (0.55-3.65)	0.464	-	-
Stage III-IV	5.13 (2.69-9.79)	<0.001	1.44 (0.21-9.70)	0.706
Non-endometrioid type	2.88 (1.47-5.60)	0.002	2.25 (0.85-5.93)	0.102
Grade 2-3	1.96 (1.00-3.84)	0.051	0.96 (0.37-2.49)	0.929
Deep myometrial invasion	4.36 (2.24-8.48)	<0.001	3.91 (1.54-9.95)	0.004
Positive lymphovascular space invasion	6.69 (3.37-13.29)	<0.01	2.24 (0.88-5.69)	0.09
Cervical involvement	3.94 (2.04-7.60)	<0.001	1.09 (0.37-3.21)	0.88
Adnexal involvement	3.10 (1.42-6.80)	0.005	0.29 (0.04-1.98)	0.206
Lymph node metastasis	6.93 (3.33-14.45)	<0.001	2.24 (0.38-13.41)	0.377
Positive peritoneal cytology	3.07 (1.16-8.09)	0.024	1.73 (0.49-6.06)	0.392
Thrombocytosis	2.34 (1.16-4.74)	0.018	2.04 (0.80-5.18)	0.135
Anemia	1.45 (0.75-2.80)	0.264	-	-

Table 4. Multivariate Analysis for Overall Survival

	Crude HR	p-value	Adjusted HR	p-value
Older age (>50 years)	0.70 (0.23-2.14)	0.526	-	-
Stage III-IV	9.11 (3.36-24.72)	<0.001	0.53 (0.17-1.66)	0.278
Non-endometrioid type	2.70 (1.00-7.31)	0.05	0.90 (0.57-1.41)	0.638
Grade 2-3	1.87 (0.69-5.06)	0.217	-	-
Deep myometrial invasion	2.78 (1.07-7.21)	0.036	1.11 (0.75-1.64)	0.615
Positive lymphovascular space invasion	10.03 (3.55-28.37)	<0.001	1.12 (0.70-1.78)	0.643
Cervical involvement	7.60 (2.89-20.00)	<0.001	1.05 (0.66-1.67)	0.843
Adnexal involvement	7.09 (2.69-18.68)	<0.001	1.79 (0.63-5.10)	0.274
Lymph node metastasis	5.43 (1.65-17.79)	0.005	4.69 (1.61-13.69)	0.005
Positive peritoneal cytology	7.15 (2.33-22.01)	0.001	0.70 (0.34-1.44)	0.327
Thrombocytosis	2.80 (1.03-7.57)	0.043	0.65 (0.40-1.04)	0.071
Anemia	3.74 (1.38-10.11)	0.009	1.54 (0.83-2.88)	0.173

4. The independent predictors for poor disease-free survival and overall survival could be determined only for deep myometrial invasion, and lymph node metastasis, respectively.

Discussion

One of the principle causes of death in patients with cancer is thromboembolism. The pathophysiological mechanisms inducing hypercoagulability in cancer patients are complex (Pieter et al., 2012). Reactive thrombocytosis is among the haemostatic abnormalities commonly observed in neoplastic diseases. It is prevalent in a wide range of malignancies and has been estimated to occur in about 10% to 57% of all patients (Sierko and Wojtukiewicz, 2004). The frequencies of thrombocytosis in patients with endometrial cancer have varied between 1.5% and 18.2% (Menczer et al., 1996; Gucer et al., 1998; Scholz et al., 2000; Tamussino et al., 2001; Ayhan et al., 2006; Metindir and Dilek, 2009). The pathophysiological mechanism of thrombocytosis in malignancy may be tumor-associated elevations of circulating platelets mediated by a direct promotion of megakaryocytopoiesis by tumor-derived humoral factors. Plasma levels of interleukin-6 and thrombopoietin have been found to be significantly elevated in patients who have thrombocytosis as compared with those who have not. Interleukin-6 is a potent stimulator of megakaryocytopoiesis and tumor cells have been shown to release IL-6 both *in vitro* and *in vivo*. In mouse models, increased hepatic thrombopoietin synthesis in response to tumor-derived interleukin-6 is an underlying mechanism of reactive thrombocytosis. Tumor-derived interleukin-6 and hepatic thrombopoietin have also been demonstrated to be linked to thrombocytosis in patients with cancer (Nakazaki, 1992; Lidor et al., 1993; Kabir and Darr, 1995; Wu et al., 1996;). Elevated levels of platelet counts have been demonstrated to be a significant prognostic factor in a variety of solid tumors, including endometrial malignancy (Menczer et al., 1996; Gucer et al., 1998; Scholz et al., 2000; Tamussino et al., 2001; Ayhan et al., 2006; Metindir and Dilek, 2009).

The prevalence of thrombocytosis in endometrial cancer found in this study (18.1%) is in agreement with previous reports (Menczer et al., 1996; Gucer et al., 1998; Scholz et al., 2000; Tamussino et al., 2001; Ayhan et al., 2006; Metindir and Dilek, 2009). Few data are currently available about the clinical relevance of anemia in endometrial cancer. In the first retrospective study by Menczer et al. (1996) only one of 66 patients with endometrial cancer (1.5%) had preoperative platelet count greater than 400000/μL in blood samples drawn prior to surgery. However, a significant correlation was found between an elevated platelet count (≥300000/μL) and unfavorable grade of differentiation and patients with an elevated count also had a poorer survival rate (Menczer et al., 1996). Subsequent studies reported higher prevalence of thrombocytosis, ranging from 7.7% to 18.2% and revealed the relation between preoperative thrombocytosis and poor prognostic factors in patients with endometrial cancer (Gucer et al., 1998; Scholz et al., 2000; Tamussino et al., 2001; Ayhan et al., 2006; Metindir and Dilek, 2009). However, the association between thrombocytosis and survival has been questionable in multivariate analyses. Gucer et al. found a significant correlation

between increasing preoperative platelet count and poor prognostic factors, such as advanced-staged disease, poorly differentiated tumor grade, deep myometrial invasion, and lymphovascular space invasion. The 5-year overall survival rate of patients with thrombocytosis was significantly worse than those with preoperative normal platelet count. However, the author did not perform a multivariate analysis of thrombocytosis (Gucer et al., 1998). Scholtz et al. also confirmed that 5-year disease-free survival and overall survival rates of patients with advanced endometrial cancer were significantly influenced by stage, cervical involvement, and thrombocytosis (Scholz et al., 2000). According to the results of Tamussino et al. thrombocytosis was associated with advanced disease, unfavorable grade, and non-endometrioid histology in the presence of anemia in endometrial cancer patients (Tamussino et al., 2001). In 2006, Ayhan et al. studied retrospectively 155 endometrial cancer patients who underwent surgical treatment consisting of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, systematic pelvic and para-aortic lymph node dissection, and peritoneal cytology. The author demonstrated that advanced stage, poor grade, the presence of cervical and adnexal involvements are associated with preoperative platelet counts in patients with endometrial cancer (Ayhan et al., 2006). Metindir et al. found that higher median preoperative platelet counts were significantly associated with the presence of cervical involvement and lymph node metastasis in the univariate but not the multivariate analyses (Metindir and Dilek, 2009). In the study by Gorelick et al. (2009) fourteen of 66 patients (18.2%) exhibited thrombocytosis and patients with advanced disease had a significant higher mean preoperative platelet count compared with patients with localized disease. However, preoperative thrombocytosis was an independent prognostic factor only in patients with advanced endometrial cancer. Among patients with early-stage disease, preoperative thrombocytosis was not associated with worsened PFS or OS (Gorelick et al., 2009). Our present data support the previous studies involving patients with endometrial cancer that thrombocytosis prior to surgery is associated with other poor prognostic factors. However, in term of disease-free survival and overall survival, the presence of thrombocytosis is shown to be a prognostic factor in the univariate but not the multivariate analyses.

In conclusion, our study reveals that thrombocytosis is not uncommon in endometrial cancer. Thrombocytosis prior to surgery is associated with other poor prognostic factors and has prognostic impact on disease-free survival and overall survival in the univariate analysis but not in the multivariate analysis.

Acknowledgements

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References

Ayhan A, Bozdaf G, TaokAran C, et al (2006). The value of preoperative platelet count in the prediction of cervical involvement and poor prognostic variables in patients with endometrial carcinoma. *Gynecol Oncol*, **103**, 902-5.

Costantini V, Zacharski LR, Moritz TE, Edwards RL (1990). The platelet count in carcinoma of the lung and colon. *Thromb Haemost*, **64**, 501-5.

Erdemir F, Kilciler M, Bedir S, et al (2007). Clinical significance of platelet count in patients with renal cell carcinoma. *Urol Int*, **79**, 111-6.

Ferlay J, Shin HR, Bray F, et al (2010). Cancer incidence and mortality worldwide; in GLOBOCAN 2008, version 1.2. IARC CancerBase No.10. Lyon, France, IARC. Availble from: http://www.dep.iarc.fr/globocan/globocan.htm.

Gorelick C, Andikyan V, Mack M, Lee YC, Abulafia O (2009). Prognostic significance of preoperative thrombocytosis in patients with endometrial carcinoma in an inner-city population. *Int J Gynecol Cancer*, **19**, 1384-9.

Gucer F, Moser F, Tamussino K, et al (1998). Thrombocytosis as a prognostic factor in endometrial carcinoma. *Gynecol Oncol*, **70**, 210-4.

Hefler L, Mayerhofer K, Leibman B, et al (2000). Tumor anemia and thrombocytosis in patients with vulvar cancer. *Tumour Biol*, **21**, 309-14.

Hernandez E, Donohue KA, Anderson LL, Heller PB, Stehman FB (2000). The significance of thrombocytosis in patients with locally advanced cervical carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol*, **78**, 137-42.

Hernandez E, Lavine M, Dunton CJ, Gracely E, Parker J (1992). Poor prognosis associated with thrombocytosis in patients with cervical cancer. *Cancer*, **69**, 2975-7.

Ikeda M, Furukawa H, Imamura H, et al (2002). Poor prognosis associated with thrombocytosis in patients with gastric cancer. *Ann Surg Oncol*, **9**, 287-91.

Kabir S, Darr GA (1995). Serum levels of interleukine-1, interleukine-6 and tumour necrosis factor-alpha in patients with gastric carcinoma. *Cancer Lett*, **95**, 207-12.

Li AJ, Madden AC, Cass I, et al (2004). The prognostic significance of thrombocytosis in epithelial ovarian carcinoma. *Gynecol Oncol*, **92**, 211-4.

Lidor YJ, Xu FJ, Martinez-Maza O, et al (1993). Constitutive production of macrophage colony-stimulating factor and interleukine-6 by human ovarian surface epithelial cells. *Exp Cell Res*, **20**, 332-9.

Menczer J, Geva D, Schejter E, Zakut H (1996). Elevated platelet count in patients with endometrial carcinoma: correlation with selected prognostic factors and with survival. *Int J Gynecol Cancer*, **6**, 463-6.

Metindir J, Dilek GB (2009). Preoperatiove hemoglobin and platelet count and poor prognostic factors in patients with endometrial carcinoma. *J Cancer Res Clin Oncol*, **135**, 125-9.

Monreal M, Fernandez-Llamazares J, Pinol M, et al (1998). Platelet count and survival in patients with colorectal cancer-a preliminary study. *Thromb Haemost*, **79**, 916-8.

Nakazaki H (1992). Preoperative and postoperative cytokines in patients with cancer. *Cancer*, **70**, 709-13.

O'Keefe SC, Marshall FF, Issa MM, Harmon MP, Petros JA (2002). Thrombocytosis is associated with a significant increase in the cancer specific death rate after radical nephrectomy. *J Urol*, **168**, 1378-80.

Pedersen LM, Milman N (1996). Prognostic significance of thrombocytosis in patients with primary lung cancer. *Eur Respir J*, **9**, 1826-30.

Pieter HR, Henri HV, Saskia M (2012). Mechanistic view of risk factors for venous thromboembolism. *Arterioscler Thromb Vasc Biol*, **32**, 563-8.

Riess L (1872). Zur pathologischen Anatomie des Blutes. *Arch*

Anat Physiol Wissensch Med, **39**, 237-49.
Scholz HS, Petru E, Gucer F, et al (2000). Preoperative thrombocytosis is an independent prognostic factor in stage III and IV endometrial cancer. *Anticancer Res*, **20**, 3983-5.
Shimada H, Oohira G, Okazumi S, et al (2004). Thrombocytosis associated with poor prognosis in patients with esophageal carcinoma. *J Am Coll Surg*, **198**, 737-41.
Sierko E, Wojtukiewicz MZ (2004). Platelets and angiogenesis in malignancy. *Semin Thromb Hemost*, **30**, 95-108.
Tamussino KF, Gucer F, Reich O, et al (2001). Pretreatment hemoglobin, platelet count and prognosis in endometrial carcinoma. *Int J Gynecol Cancer*, **11**, 236-40.
Taucher S, Salat A, Gnant M, et al (2003). Impact of pretreatment thrombocytosis on survival in primary breast cancer. *Thromb Haemost*, **89**, 1098-106.
Wu CW, Wang SR, Chao MF, et al (1996). Serum interleukine-6 levels reflect disease status of gastric cancer. *Am J Gastroenterol*, **91**, 1417-22.
Zeimet AG, Marth C, Muller-Holzner E, Daxenbichler G, Dapunt O (1994). Significance of thrombocytosis in patients with epithelial ovarian cancer. *Am J ObstetGynecol*, **170**, 549-54.