

## RESEARCH ARTICLE

# Do Leukocyte and Platelet Counts Have Benefit for Preoperative Evaluation of Endometrial Cancer?

Huseyin Ekici<sup>1</sup>, Erdal Malatyalioglu<sup>2</sup>, Arif Kokcu<sup>2</sup>, Emel Kurtoglu<sup>2\*</sup>, Migraci Tosun<sup>2</sup>, Handan Celik<sup>2</sup>

## Abstract

**Purpose:** The aim of this study was to investigate the association between preoperative leukocyte and platelet counts and the stage of the disease in patients with endometrial cancer. **Materials and Methods:** Data for 100 patients undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy for benign uterine diseases and 177 patients surgically staged for endometrial cancer at Ondokuz Mayıs University, Department of Gynecology and Obstetrics between 2005 and 2013, with preoperative complete blood count in the week prior to surgery including WBC, platelet count, pathologic evaluation for both benign and malign endometrium lesions, tumor stage and presence of lymphovascular space invasion (LVI), were retrospectively analyzed. **Results:** The preoperative leukocyte count was significantly higher in patients with endometrial cancer when compared to the patients with benign diseases. However, there were no significant differences in platelet counts between the groups. Patients with advanced stage endometrial cancer had higher preoperative leukocyte counts when compared to the early stage disease whereas there was no difference in platelet count. Multivariate regression analysis identified preoperative leukocytosis as an independent prognostic factor for endometrial cancer. The optimal cut-off point for WBC was calculated as 10,500 to differentiate stage 1-2-3 and 4 with 88.9% sensitivity and 86.3% specificity (AUC: 0.901, 95% CI: 0.829-0.973,  $p < 0.001$ , PPV: 25.8%, NPV: 99.3%). **Conclusions:** Preoperative leukocytosis is independently associated with advanced endometrial cancer.

**Keywords:** Endometrial cancer - leukocytosis - prognosis - stage - thrombocytosis

*Asian Pac J Cancer Prev*, 16 (13), 5305-5310

## Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries (Ferlay et al., 2012). Staging surgery which consists of peritoneal washing, total hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node (PLN) dissection with or without paraaortic lymph node (PALN) dissection remains the cornerstone in primary treatment for endometrial cancer (Pecorelli, 2009). Prognostic factors have been investigated by several studies, as a result of which, FIGO (The International Federation of Gynecology and Obstetrics) stage, myometrial invasion, histologic subtype and grade and lymphovascular involvement were found to be the most important ones (Prat, 2004; Amant et al., 2005). Furthermore, alterations in preoperative hematologic parameters such as leukocytosis and thrombocytosis have been suggested to be prognostic biomarkers and independently associated with advanced disease (Gorelick et al., 2009; Worley et al., 2012; Njolstad et al., 2013).

The aim of this study was to evaluate the significance of preoperative leukocytosis and thrombocytosis among patients with endometrial cancer.

## Materials and Methods

The study included the patients (cancer group) surgically staged for endometrial cancer according to FIGO 2009 guidelines which consisted of peritoneal cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, systemic pelvic and para-aortic lymphadenectomy (Pecorelli, 2009), and the patients (control group) underwent total abdominal or vaginal hysterectomy for benign uterine diseases such as endometrial polyp, fibroid, uterine prolapsus at Ondokuz Mayıs University, Department of Gynecology and Obstetrics between 2005 and 2013.

Patients were excluded from this study if any of the following were present: incompletely staged surgery, second malignancies, hematological disease, inflammatory disease, autoimmune disease, recombinant granulocyte colony-stimulating factor use, prior chemotherapy or radiotherapy, hypertension, diabetes mellitus, metabolic syndrome, nephropathy, renal or hepatic dysfunction, left ventricular dysfunction, valvular heart disease, abnormal thyroid function tests, previous history of local or systemic infection, HIV infection, any medication that is related to

<sup>1</sup>Kackar State Hospital, Rize, Turkey, <sup>2</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey \*For correspondence: emel0022@mynet.com

patients' inflammatory condition such as corticosteroids and missing preoperative complete blood cell count or complete blood count drawn more than two weeks prior to surgery.

Patients' preoperative and postoperative data, including demographic features, complete blood count in the week prior to surgery with differentials including WBC, platelet count, histopathologic evaluations for both benign and malign endometrium lesions, grade of endometrial cancer, tumor stage, tumor size, presence of

lymphovascular space invasion (LVI) and overall survival were retrospectively analyzed. Leukocytosis was defined as white blood cell count of >10.000 cells/mm<sup>3</sup>, and thrombocytosis was defined as thrombocyte count of >450 X 10<sup>3</sup> platelets/mm<sup>3</sup>.

Data analysis was performed by using SPSS for Windows, version 11.5. Whether the distributions of continuous and intermittent variables were normally or not was determined by Kolmogorov Smirnov test. Homogeneity of variances was analyzed by Levene test.

**Table 1. Preoperative PLT and WBC Counts According to Clinico-Pathological Features of the Cancer Group**

Features	Pre-op PLT (x10 <sup>3</sup> /mm <sup>3</sup> )	Pre-op WBC (cell/mm <sup>3</sup> )
Grade		
I	281 (163-732)a	6995 (3620-15400)a
II	279 (164-542)b	7900 (4000-16100)
III	327.5 (221-742)a.b	8830 (4900-16100)a
p-value †	0.023	0.035
Histology		
Non-endometrioid	293.5 (212-742)	8475 (4600-15270)
Endometrioid	283 (163-732)	7450 (3620-16100)
p-value ‡	0.124	0.024
Tumor size		
<1 cm	283.5 (163-742)	7710 (3620-16100)
1-2 cm	296 (274-385)	8760 (5140-16100)
p-value ‡	0.313	0.525
Myometrial invasion		
<50%	278 (163-732)	7300 (3620-14940)
>50%	296 (165-742)	8250 (4000-16100)
p-value ‡	0.161	0.099
Cervical involvement		
Negative	280 (163-732)	7500 (3620-16100)
Positive	304.5 (179-742)	8000 (4620-16100)
p-value ‡	0.013	0.091
Adnexal involvement		
Negative	281 (163-732)	7480 (3620-16100)
Positive	349 (177-742)	10700 (6060-16100)
p-value ‡	0.053	<0.001
Peritoneal cytology		
Nondiagnostic	276.5 (163-625)	7500 (3810-16100)
Negative	203.5 (164-732)	7785 (3620-14940)
Positive	317 (217-742)	8760 (6350-16100)
p-value †	0.078	0.067
Lymphovascular invasion		
Negative	279 (163-732)	7415 (3620-15400)
Positive	311 (188-742)	9180 (5130-16100)
p-value ‡	0.003	<0.001
Pelvic lymph node metastasis		
Negative	282 (163-732)	7460 (3620-16100)
Positive	314.5 (211-742)	9240 (4600-16100)
p-value ‡	0.039	0.003
Paraaortic lymph node metastasis		
Negative	283 (163-732)	7500 (3620-15410)
Positive	306 (188-742)	10245 (4600-16100)
p-value ‡	0.176	0.003
Stage		
I	280 (163-732)	7415 (3620-15410)a.b
II	286.5 (179-434)	7195 (4620-14200)c.d
III	306 (177-542)	8945 (4600-16100)a.c.e
IV	355 (268-742)	11100 (8540-16100)b.d.e
p-value†	0.067	<0.001

†Kruskal Wallis test. ‡ Mann Whitney U test. a: Significant difference between Grade I and Grade III (p=0.009). b: Significant difference between Grade II and Grade III (p=0.005); †Kruskal Wallis test. ‡ Mann Whitney U test. a: Significant difference between stage I and III (p=0.006). b: Significant difference between stage I and IV (p<0.001). c: Significant difference between stage II and III (p=0.008). d: Significant difference between stage II and IV (p<0.001). e: significant difference between stage III and IV (p=0.017).

Data for continuous and intermittent numeric variables were shown as mean  $\pm$  SD or median (min-max), data for categorical variables were shown as percentage (%) and case number where applicable.

The significance of differences between the groups were evaluated by one way variant analysis (One-Way ANOVA). Mann Whitney U test was applied for comparisons of the median values between two independent groups, whereas Kruskal Wallis test was used in case of the presence of more than two groups to compare. Conover's multiple comparison test was applied in order to determine the factors causing the difference, if there was a significance in Kruskal Wallis test statistics. Categorical variables were evaluated by Pearson's Chi-square, Fisher's exact or Likelihood Ratio test, where applicable.

To determinate whether preoperative WBC and PLT were significant to discriminate the groups in terms of clinical features, ROC analysis was applied and area under curve and 95% confidence interval was calculated. The maximum sum of sensitivity and specificity for the significant test result. Sensitivity, specificity, positive and negative predictive values were also calculated at the best cut-off points.

Determining whether the cut-off points of WBC and PLT were significant to discriminate stage 1 and stage 2, 3, 4 in order from each other was evaluated by Multiple Logistic Regression analysis. Any variable whose univariable test had a p value  $<0.25$  was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Adjusted odds ratios, 95% confidence intervals and wald statistics also were calculated.

A p value less than 0.05 was considered statistically significant.

## Results

The study included 177 patients diagnosed with endometrial cancer and underwent surgical staging, and 100 patients with hysterectomy and bilateral salpingo-oophorectomy for benign gynecological indications. The mean age of the patients with endometrial

cancer was  $59.6 \pm 10.8$ . A hundred and forty five (81.9%) of the endometrial cancers was endometrioid type, 32 (18.1%) of them were non-endometrioid. Eighty eight (49.7%) of the cancer cases was classified as grade I, 67 (37.9%) of them was grade II, and the rest of 22 (12.4%) was grade III. When myometrial invasion was evaluated, it was  $<50\%$  in 94 (53.1%) patients and  $>50\%$  in 83 (46.9%) of cases. Cervical involvement was present in 42 cases (23.7%) whereas adnexal involvement was in only 17 patients (9.6%). Peritoneal cytology was positive in only 13 (7.3%) patients while negative in 84 (47.5%) cases and nondiagnostic in 80 (45.2%) cases. Lymphovascular invasion was detected in 29 (16.4%) patients. Pelvic lymph node metastasis was present in 22 (12.4%) cases while paraaortic metastasis was present in 16 (9%) patients. When stage of endometrial cancers was determined, there were 118 (66.7%) patients with stage I, 24 (13.6%) cases with stage II, 26 (14.7%) patients with stage III and only nine (5.1%) cases with advanced stage IV.

When clinicopathologic features were compared between two groups, preoperative leukocyte count was significantly higher in patients with endometrial cancer (preoperative WBC count in cancer group:  $8100 \pm 2668$  cell/mm<sup>3</sup>, in control group:  $7039 \pm 1474$  cell/mm<sup>3</sup>,  $p < 0.001$ ), while there was no significant difference in preoperative platelet count between the groups; preoperative PLT count in cancer group:  $302 \pm 91 \times 10^3$ /mm<sup>3</sup>, in control group:  $295 \pm 75 \times 10^3$ /mm<sup>3</sup>,  $p < 0.05$ ).

When patients' clinicopathologic features were evaluated in terms of correlation with preoperative mean leukocyte and platelet counts; mean leukocyte count was significantly higher in the presence of grade 3 disease, non-endometrioid histology, adnexal involvement, lymphovascular invasion, pelvic and paraaortic metastasis and advanced stage ( $p < 0.05$ ) (Table 1). ROC analyses revealed significant area under curve for WBC count in differentiation of increased grade, adnexal involvement, positive peritoneal cytology, lymphovascular invasion, pelvic and paraaortic lymph node metastasis and advanced stage (Table 2). The optimal cut-off points were calculated for preoperative WBC count to discriminate the clinical features of endometrial cancer cases (Table 3). It was found as 6915 to differentiate stage 1 and advanced stages

**Table 2. ROC Analyses for pre-op WBC to Differentiate Clinico-Pathological Features of Endometrial Cancers**

Features	AUC	95% Confidence interval	p-value
Grade 1 vs 2-3	0.592	0.508-0.676	0.034
Grade 1-2 vs 3	0.643	0.512-0.774	0.030
Histology	0.628	0.534-0.722	0.024
Tumor size	0.571	0.319-0.823	NS
Myometrial invasion	0.572	0.487-0.657	NS
Cervical involvement	0.587	0.488-0.685	NS
Adnexal involvement	0.773	0.664-0.882	$<0.001$
Positive peritoneal cytology	0.690	0.545-0.835	0.028
Lymphovascular invasion	0.711	0.608-0.814	$<0.001$
Pelvic lymph node metastasis	0.694	0.565-0.822	0.003
Paraaortic lymph node metastasis	0.727	0.581-0.873	0.003
Stage 1 vs 2-3-4	0.620	0.530-0.710	0.009
Stage 1-2 vs 3-4	0.739	0.641-0.837	$<0.001$
Stage 1-2-3 vs 4	0.901	0.829-0.973	$<0.001$

\*AUC: Area under curve

**Table 3. Optimal Cut-Off Points for Pre-op WBC Counts to Differentiate the Clinico-Pathological Features of Endometrial Cancer Cases**

Features	Cut-off	Sensitivity	Specificity	PPV	NPV
Grade 1 vs 2-3	>7785	60.7%	61.4%	61.4%	60.7%
Grade 1-2 vs 3	>8020	72.7%	58.7%	20.0%	93.8%
Histology	<6665	38.6%	90.6%	94.9%	24.6%
Adnexal involvement	>8475	82.4%	65.6%	20.3%	97.2%
Positive peritoneal cytology	>6345	100.0%	32.1%	18.6%	100.0%
Lymphovascular invasion	>8390	72.4%	66.2%	29.6%	92.5%
Pelvic lymph node metastasis	>8475	68.2%	65.2%	21.7%	93.5%
Paraortic lymph node metastasis	>8475	75.0%	64.6%	17.4%	96.3%
Stage 1 vs 2-3-4	>6915	72.9%	48.3%	41.3%	78.1%
Stage 1-2 vs 3-4	>8475	71.4%	69.0%	36.2%	90.7%
Stage 1-2-3 vs 4	>10500	88.9%	86.3%	25.8%	99.3%

\*PPV: Positive predictive value, NPV: Negative predictive value

**Table 4. Determination of the Most Definitive Risk Factors Including Pre-op WBC Count in Discrimination of Stage I Endometrium Cancer from Stage II, III and IV in Order According to Multivariate Logistic Regression Analysis**

	Odds ratio	95% Confidence interval		Wald	p-value
Stage II					
Grade 2	2,114	0.789	5,666	2,215	0.137
Grade 3	1,724	0.260	11,416	0.319	0.572
Endometrioid	1,478	0.387	5,637	0.327	0.567
Myometrial invasion	5,545	1,940	15,853	10,216	<0.001
Lymphovascular invasion	1,363	0.315	5,903	0.171	0.679
Pre-op WBC >10500	0.355	0.041	3,031	0.897	0.344
Stage III					
Grade 2	2,761	0.916	8,324	3,254	0.071
Grade 3	6,010	1,236	29,232	4,939	0.026
Endometrioid	3,210	0.955	10,789	3,555	0.059
Myometrial invasion	3,707	1,245	11,036	5,541	0.019
Lymphovascular invasion	2,510	0.645	9,766	1,763	0.184
Pre-op WBC >10500	3,918	1,150	13,352	4,767	0.029
Stage IV					
Grade 2	1,496	0.040	56,440	0.047	0.828
Grade 3	42,940	0.9999	1,844,004	3,841	0.050
Endometrioid	19,950	1,135	350,663	4,188	0.041
Myometrial invasion	1,149	0.044	29,831	0.007	0.933
Lymphovascular invasion	9,723	0.327	288,805	1,728	0.189
Pre-op WBC >10500	228,499	5,679	9,194,156	8,302	0.004

with 72.9% sensitivity and 48.3% specificity (AUC: 0.620, 95% CI: 0.530-0.710,  $p=0.009$ , PPV: 41.3%, NPV: 78.1%), the optimal cut-off point for WBC was calculated as 8475 to differentiate stage 1-2 and 3-4 with 71.4% sensitivity and 69% specificity (AUC: 0.739, 95% CI: 0.641-0.837,  $p<0.001$ , PPV: 36.2%, NPV: 90.7%) (Table 3). In addition, the optimal cut-off point for WBC was calculated as 10500 to differentiate stage 1-2-3 and 4 with 88.9% sensitivity and 86.3% specificity (AUC: 0.901, 95% CI: 0.829-0.973,  $p<0.001$ , PPV: 25.8%, NPV: 99.3%).

Platelet count was found to be significantly increased in the presence of grade 3 disease, cervical involvement, lymphovascular invasion and pelvic lymph node metastasis ( $p<0.05$ ). There was no significant association between preoperative platelet counts and stage of endometrial cancer (Table 1).

When most definitive risk factors in differentiation of advanced stages (stage II, III and IV), only myometrial

invasion was identified as an independent risk factor in discrimination of stage II from stage I ( $p<0.001$ ). Increased histopathologic grade (grade 3), myometrial invasion and pre-op WBC count  $>10500$  (cell/mm<sup>3</sup>) were found to be independent risk factors in discrimination of stage III from stage I ( $p=0.026$ ,  $p=0.019$ ,  $p=0.029$ ). Endometrioid histology and pre-op WBC count  $>10500$  (cell/mm<sup>3</sup>) were identified as independent risk factors in discrimination of stage IV from stage I ( $p=0.041$ ) (Table 4).

## Discussion

Preoperative hematological alterations such as anemia, leukocytosis and thrombocytosis have been associated with poor prognosis in different malignancies (Hefler et al., 2000; Pedersen and Milman., 2003; Chen et al., 2005; Brockmann et al., 2007; Lu et al., 2007). Although the exact mechanism remains unclear, studies suggested that

tumors can affect hematologic parameters by significant tumor bleed, infiltrating the bone marrow or by producing proinflammatory cytokines (Weiss and Goodnough, 2005). Prognostic value of these parameters have been recently investigated in gynecological malignancies and findings have shed new light to such mechanisms, Pretreatment leukocytosis was associated with advanced disease in cervical cancer when compared to patients without leukocytosis (Garcia-Arias et al., 2007; Mabuchi et al., 2011). Up-regulation of hematopoietic growth factors, such as G-CSF, GM-CSF, IL-1, IL-6 and TNF-alpha were suggested to play a critical role in tumor-related leukocytosis (Sato et al., 1987; Chen et al., 1995; Watanabe et al., 1998; Mabuchi et al., 2011). G-CSF, which was suspected to be the most influential, was found significantly elevated in cervical cancer patients with pretreatment leukocytosis (Mabuchi et al., 2011). Not only in cervical cancer, but also in ovarian cancer, preoperative leukocytosis has been recently associated with poor prognosis (So et al., 2014).

With respect to endometrial cancer, when factors such as stage, histopathologic type, lymphovascular invasion, myometrial invasion and lymph node metastasis, affecting prognosis of the disease were evaluated with multivariate analysis, studies demonstrated preoperative leukocytosis as an independent risk factor for malignant endometrial lesions, advanced stage endometrial cancer and decreased survival (Worley et al., 2012; Luomaranta et al., 2013; Worley et al., 2013; Acmaz et al., 2014). In the present study, preoperative leukocytosis was found to be significantly associated with increased grade, non-endometrioid histology, cervical involvement, positive peritoneal cytology, lymphovascular invasion, pelvic and paraaortic lymph node metastasis and advanced stage (Table 2). Furthermore, optimal cut-off for pre-op WBC level was determined to differentiate advanced stage disease (Table 3).

Thrombocytosis, which is an other prevalent hematological alteration, has been estimated to occur in about 10%-57% of all patients diagnosed with malignant disease (Sierko and Wojtukiewicz, 2004). Since the responsible mechanism for thrombocytosis in malignancy is poorly understood, some factors are accepted as contributors to this process. One of them is production of cytokines such as IL-6 and IL-1 and stimulation of megakaryocytes and their precursors (Burststein and Harker, 1983; Blay et al., 1992). An other one is that elevated platelets may enhance the aggressive behaviour of tumor and shield it from immune system detection. In addition, platelets may promote angiogenesis through some platelet-derived factors such as vascular growth factor, thrombospondin and endostatin (Karparkin S, Pearlstein, 1981; Verheul and Pinedo, 1998). Recently, studies have investigated the relationship between thrombocytosis and gynecological cancers (Hernandez et al., 1992; Hefler et al., 2000; Lerner et al., 2007; Gorelick et al., 2009). With respect to endometrial cancer, although preoperative elevated platelet count was associated with poor differentiation in grade, advanced stage, lymph node metastasis, adnexal and cervical involvement in, thrombocytosis was not found an independent prognostic

factor in the multivariate studies (Gucer et al., 1998; Ayhan et al., 2006; Metindir and Bilir, 2009; Heng and Benjapibal, 2014). In contrast, there have been studies reporting preoperative thrombocytosis as an independent prognostic factor in endometrial cancer (Scholz et al., 2000; Tamussino et al., 2001; Gorelick et al., 2009). In this study, there was no significant difference in preoperative platelet count between the patients with endometrial cancer and the control group.

Despite the studies aimed to determine whether or not preoperative leukocytosis and thrombocytosis are independent risk factors on the stage of endometrial cancer, the topic has been controversial. In the present study, pre-op WBC count >10500 (cell/mm<sup>3</sup>) were found to be independent risk factors in discrimination of stage III from stage I (p=0.026, p=0.019, p=0.029) and stage IV from stage I (p=0.041) (Table 4). However, thrombocytosis was not determined as an independent risk factor on the stage of the disease.

The current study has some limitations inherit to its retrospective design. First, surgical procedures were not standardized with respect to lymphadenectomy. Second, overall and disease free survival were not reported due to the lack of communication with the patients.

In conclusion, preoperative leukocytosis (WBC >10500 cell/mm<sup>3</sup>) was independently associated with advanced endometrial cancer. More detailed studies could help to clarify the exact mechanism behind pretreatment leukocytosis and the impact of it on clinical outcomes.

## References

- Acmaz G, Aksoy H, Unal D, et al (2014). Are neutrophil/lymphocyte and platelet/lymphocyte ratios associated with endometrial precancerous and cancerous lesions in patients with abnormal uterine bleeding? *Asian Pac J Cancer Prev*, **15**, 1689-92.
- Amant F, Moerman P, Neven P, et al (2005). Endometrial cancer. *Lancet*, **366**, 491-505.
- Ayhan A, Bozdag G, Taskiran 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.
- Blay JY, Negrier S, Combaret V, et al. (1992). Serum level of interleukin 6 as a prognosis factor in metastatic renal cell carcinoma. *Cancer Res*, **15**, 3317-22.
- Brockmann MA, Giese A, Mueller K, et al (2007). Preoperative thrombocytosis predicts poor survival in patients with glioblastoma. *Neuro Oncol*, **9**, 335-42
- Burststein SA, Harker LA. (1983). Control of platelet production. *Clin Haematol*, **12**, 3-22.
- Chen YM, Whang-Peng J, Liu JM, et al. (1995). Leukemoid reaction resulting from multiple cytokine production in metastatic mucoepidermoid carcinoma with central necrosis. *Jpn J Clin Oncol*, **25**, 168-72.
- Chen CC, Yang CF, Yang MH, et al (2005). Pretreatment prognostic factors and treatment outcome in elderly patients with de novo acute myeloid leukemia. *Ann Oncol*, **16**, 1366-73.
- Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, et al (2012). GLOBOCAN Cancer incidence and mortality worldwide: IARC cancer base No. 11 [Internet]. Lyon, France: International Agency Res Cancer, 2013.
- Garcia-Arias A, Cetina L, Candelaria M, Robles E, Dueñas-

- González A. (2007). The prognostic significance of leukocytosis in cervical cancer. *Int J Gynecol Cancer*, **17**, 465-70.
- 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.
- Heng S, Benjapibal M. (2014). Preoperative thrombocytosis and poor prognostic factors in endometrial cancer. *Asian Pac J Cancer Prev*, **15**, 10231-6.
- 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.
- Karpatkin S, Pearlstein E. (1981). Role of platelets in tumor cell metastases. *Ann Intern Med*, **95**, 636-41.
- Lerner DL, Walsh CS, Cass I, Karlan BY, Li AJ (2007). The prognostic significance of thrombocytosis in uterine papillary serous carcinomas. *Gynecol Oncol*, **104**, 91-4.
- Lu CC, Chang KW, Chou FC, Cheng CY, Liu CJ. (2007). Association of pretreatment thrombocytosis with disease progression and survival in oral squamous cell carcinoma. *Oral Oncol*, **43**, 283-8.
- Luomaranta A, Leminen A, Loukovaara M. (2013). Prediction of lymph node and distant metastasis in patients with endometrial carcinoma: a new model based on demographics, biochemical factors, and tumor histology. *Gynecol Oncol*, **129**, 28-32.
- Mabuchi S, Matsumoto Y, Isohashi F, et al (2011). Pretreatment leukocytosis is an indicator of poor prognosis in patients with cervical cancer. *Gynecol Oncol*, **122**, 25-32.
- Metindir J, Bilir Dilek G. (2009). Preoperative hemoglobin and platelet count and poor prognostic factors in patients with endometrial carcinoma. *J Cancer Res Clin Oncol*, **135**, 125-9.
- Njolstad TS, Engerud H, Werner HM, Salvesen HB, Trovik J (2013). Preoperative anemia, leukocytosis and thrombocytosis identify aggressive endometrial carcinomas. *Gynecol Oncol*, **131**, 410-5.
- Pecorelli S (2009). Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*, **105**, 103-4.
- Pedersen LM, Milman N (2003). Diagnostic significance of platelet count and other blood analyses in patients with lung cancer. *Oncol Rep*, **10**:213-6.
- Prat J (2004). Prognostic parameters of endometrial carcinoma. *Hum Pathol*, **35**, 649-62.
- Sato K, Fujii Y, Ono M, Nomura H, Shizume K (1987). Production of interleukin 1 alpha-like factor and colony-stimulating factor by a squamous cell carcinoma of the thyroid (T3M-5) derived from a patient with hypercalcemia and leukocytosis. *Cancer Res*, **15**, 6474-80.
- Scholz HS, Petru E, Guce F, et al (2000). Preoperative thrombocytosis is an independent prognostic factor in stage III and IV endometrial cancer. *Anticancer Res*, **20**, 3983-5.
- Sierko E, Wojtukiewicz MZ (2004). Platelets and angiogenesis in malignancy. *Semin Thromb Hemost*, **30**, 95-108.
- So KA, Hong JH, Jin HM, et al (2014). The prognostic significance of preoperative leukocytosis in epithelial ovarian carcinoma: a retrospective cohort study. *Gynecol Oncol*, **132**, 551-5.
- Tamussino KF, Guce F, Reich O, et al (2001). Pretreatment hemoglobin, platelet count, and prognosis in endometrial carcinoma. *Int J Gynecol Cancer*, **11**, 236-40.
- Verheul HM, Pinedo HM. (1998). Tumor Growth: a putative role for platelets? *Oncologist*, **3**, 2.
- Watanabe M, Ono K, Ozeki Y, et al. (1998). Production of granulocyte-macrophage colony-stimulating factor in a patient with metastatic chest wall large cell carcinoma. *Jpn J Clin Oncol*, **28**, 559-62.
- Weiss G, Goodnough LT. (2005). Anemia of chronic disease. *N Engl J Med*, **352**, 1011-23.
- Worley MJ Jr, Nitschmann CC, Shoni M, et al (2012). The significance of preoperative leukocytosis in endometrial carcinoma. *Gynecol Oncol*, **125**, 561-5.