RESEARCH ARTICLE

# Presence of Anemia and Poor Prognostic Factors in Patients with Endometrial Carcinoma

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## Abstract

**This study evaluated the relationship between pretreatment hemoglobin (Hb) and prognostic factors in Thai patients with endometrial cancer. Medical records of 228 patients who had undergone surgery between January 2005 and December 2007 were retrospectively reviewed. Associations between clinicopathological variables and pretreatment Hb levels were described using Pearson's chi square test or two-tailed Fisher's exact test. Survival analysis was performed with Kaplan-Meier estimates. Univariate and Cox-regression models were used to evaluate the prognostic impact of various factors, including Hb levels, in term of disease-free survival. The median duration of follow-up was 38.2 months. Eighty-nine patients (39%) had a preoperative Hb level of <12 g/dL, these having significantly higher rates of non-endometrioid histology, advanced FIGO stage, lymphovascular space invasion, cervical involvement, adnexal involvement, positive peritoneal cytology, and lymph node involvement than patients with Hb ≥12 g/dL. The 5-year disease-free and overall survival were significantly lower in patients with pretreatment Hb levels <12 g/dL compared with those with Hb ≥12 g/dL (79.3% vs. 89.2%, p=0.044 and 87.6% vs. 99.3%, p<0.001, respectively). In the multivariate analysis only histology, myometrial invasion, and lymphovascular invasion proved to be independent prognostic factors, whereas tumor grading, stage, cervical involvement, adnexal involvement, positive peritoneal cytology, lymph node involvement, and low Hb were not. In conclusion, presence of anemia before treatment may reflect poor prognostic factors in patients with endometrial cancer and low pretreatment hemoglobin level may have a prognostic impact on clinical outcome.**

**Keywords:** Anemia - prognostic factors - endometrial cancer

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## Introduction

Anemia (generally defined as Hb level below 12 g/dL) is a common condition in patients who have cancer. Its prevalence varies widely, ranging from 30% to 90% of patients with cancer, depending on the type of cancer. Gynecological malignancies are among the tumors characterized by a higher prevalence of anemia at diagnosis (Ludwig et al., 2004; Seshadri et al., 2005, Achariyapota et al., 2010). Besides worsening the quality of life, the presence of anemia itself has been found to be a poor prognostic variable and is associated with shorter survival times for several cancers (Caro et al., 2001; Van Belle et al., 2003; Alici et al., 2006).

Endometrial cancer is the most common cancer of the female genital tract in developed countries. Most patients present with postmenopausal vaginal bleeding and the majority of endometrial cancers are diagnosed while the disease is limited to the uterine corpus. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the cornerstone of treatment. 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 about the clinical relevance of anemia in endometrial cancer. This study was undertaken to evaluate the relationship between pretreatment Hb and prognostic factors in Thai women with endometrial cancer.

## Materials and Methods

We retrospectively reviewed the hospital records of patients with with histologically confirmed endometrial cancer who underwent primary surgery at the Department of Obstetrics and Gynecology, Siriraj Hospital, between January 2005 and December 2007. Criteria for inclusion in the study were as follows: age <80 years, no past or present secondary malignancy, no other nonmalignancy-associated anemia (e.g. thalassemia or chronic iron deficiency anemia). Surgery consisted of total hysterectomy with bilateral salpingo-oophorectomy and peritoneal washing for cytology. One hundred and eight-nine patients with 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) underwent pelvic or pelvic and para-aortic lymphadenectomy. The tumor stage and histological diagnosis of each case were surgically determined according to the criteria of the International

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Federation of Gynecology and Obstetrics (FIGO staging system, 1989) 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 histologic factors received no adjuvant treatment. Accordingly, 93 received radiation only, 25 received chemotherapy only, 7 received both radiation and chemotherapy, and 103 received no adjuvant treatment.

Baseline hemoglobin level in each patient was determined 24-48 hours before the surgery. Patients were divided into 2 groups based on the Common Toxicity Criteria from the National Cancer Institute which were patients with normal Hb value (≥12 g/dL) and patients with anemia (<12 g/dL). Association between clinicopathological variables (histology, grading, stage, myometrial invasion, lymphovascular space invasion, cervical involvement, adnexal involvement, peritoneal cytology, and lymph node status) and pretreatment Hb levels 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 Hb levels in terms of disease-free survival.

A p-value of <0.05 was taken for statistical significance. Data management and statistics were performed using SPSS software for Windows version 18. 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

Two hundreds and twenty-eight patients with endometrial cancer qualified for inclusion in the study. The mean age of patient at diagnosis was 57.8 years (median 56.5; SD 10.3). Histologically, while 194 (85.1%) patients were endometrioid, the remaining 34 (14.9%) had non-endometrioid histology. Tumor grade among 194 patients with endometrioid histology was G1 in 120 (61.9%) patients, G2 in 52 (26.8%), and G3 in 22 (11.3%). Stage of the disease was early in the majority of the patients (65.8% stage 1, 9.6% stage 2). Approximately one third of the patients had deep myometrial invasion. Thirty-eight (17.4%) of the 219 patiens was found to have lymphovascular space invasion. Cervical and adnexal involvement was observed in 46 (20.2%) and 27 (11.8%) patients, respectively. Nineteen (11.0%) of the 191 patients had positive peritoneal cytology. Among 189 patients who underwent lymphadenectomy, 23 (12.2%) had nodal involvement, and the remaining did not. The median duration of follow-up was 38.2 months (range, 0.3-70.1 months) and mean overall survival was 66.5 months (95% confidence interval, 0.3-70.1 months). The overall 5-year survival probability was 94.7%. At the end of the observation period, 188 patients (82.5%) were tumor free, 26 patients (11.4%) were alive with tumor, 12 patients (5.2%) had died of their disease and 2 patients (0.9%) had died from non-cancer related conditions.

Correlation between anemia and baseline patients' characteristics are given in Table 1. Overall mean hemoglobin level before surgery was 12.3 g/dl (SD 1.6). After classification, 139 (61%) patients had normal Hb level (≥12 g/dL), while the remaining 89 (39%) showed some degree of anemia. These 89 patients had significant higher rates of nonendometrioid histology, advanced FIGO stage, lymphovascular space invasion, cervical involvement, adnexal involvement, positive peritoneal cytology, and lymph node involvement than patients with Hb ≥12 g/dL. The 5-year disease-free and overall survival were significantly lower in patients with pretreatment Hb levels <12 g/dL compared with those with Hb ≥12 g/dL (79.3% vs. 89.2%, p =0.044 and 87.6% vs. 99.3%, p <0.001, respectively) (Figure 1A, 1B). Univariate analysis demonstrated a significant influence of all prognostic variables in term of 5-year disease-free survival. However in multivariate analyses, the significance prognostic factors could be determined only for histology, myometrial

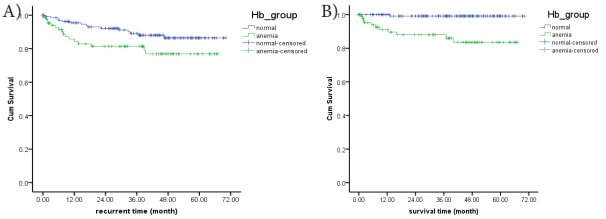


**Figure 1. A) Disease-Free Interval. B) Overall Survival.**

**Table 1. Baseline Patients' Characteristics**

| | Pretreatment Hb levels | | p-value |
|---|---|---|---|
| | Anemia (N=89) | Normal (N=139) | |
| Histology | | | |
| Endometrioid | 67 (75.3%) | 127 (91.4%) | **0.002** |
| Nonendometrioid | 22 (24.7%) | 12 (8.6%) | |
| Grading (n = 194) | | | |
| G1 | 43 (64.2%) | 77 (60.6%) | 0.546 |
| G2 & G3 | 24 (35.8%) | 50 (39.4%) | |
| Stage | | | |
| I and II | 54 (60.7%) | 118 (84.9%) | **<0.001** |
| III and IV | 35 (39.3%) | 21 (15.1%) | |
| Myometrial invasion | | | |
| < 50% | 57 (64.0%) | 99 (71.2%) | 0.321 |
| ≥ 50% | 32 (36.0%) | 40 (28.8%) | |
| Lymphovascular space invasion (n = 219) | | | |
| Positive | 21 (25.0%) | 17 (12.6%) | **0.03** |
| Negative | 63 (75.0%) | 118 (87.4%) | |
| Cervical involvement | | | |
| Positive | 27 (30.3%) | 19 (13.7%) | **0.004** |
| Negative | 62 (69.7%) | 120 (86.3%) | |
| Adnexal involvement | | | |
| Positive | 20 (22.5%) | 7 (5.0%) | **<0.001** |
| Negative | 69 (77.5%) | 132 (95.0%) | |
| Peritoneal cytology (n = 191) | | | |
| Positive | 10 (14.7%) | 9 (7.3%) | 0.167 |
| Negative | 58 (85.3%) | 114 (92.7%) | |
| Lymph node status (n = 189) | | | |
| Positive | 17 (23.3%) | 6 (5.2%) | **0.001** |
| Negative | 56 (76.7%) | 110 (94.8%) | |

**Table 2. Univariate and Multivariate Analysis with Regard to Disease-Free Interval**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | p-value | Adjusted HR | 95%CI | p-value |
| Histology (nonendometrioid vs endometrioid) | 2.98 | 1.40-6.33 | **0.005** | 4.41 | 1.16-16.84 | **0.03** |
| Grading (G1 vs G2/G3) | 2.67 | 1.11-6.46 | **0.029** | 1.43 | 0.53- 4.61 | 0.517 |
| Stage (advanced vs early) | 7.89 | 3.77-16.50 | **<0.001** | 2.28 | 0.51-10.14 | 0.278 |
| Myometrial invasion (≥50% vs <50%) | 6.5 | 2.99-14.13 | **<0.001** | 11.06 | 2.83-43.18 | **0.001** |
| LVSI (positive vs negative) | 10.43 | 4.87-22.37 | **<0.001** | 3.25 | 1.18-8.95 | **0.023** |
| Cervical involvement (positive vs negative) | 4.89 | 2.39-10.01 | **<0.001** | 1.45 | 0.50-4.24 | 0.493 |
| Adnexal involvement (positive vs negative) | 2.7 | 1.10-6.61 | **0.03** | 2.46 | 0.49-12.45 | 0.277 |
| Peritoneal cytology (positive vs negative) | 5.51 | 2.15-14.12 | **<0.001** | 1.1 | 0.30-3.99 | 0.89 |
| Lymph node (positive vs negative) | 10.42 | 4.71-23.04 | **<0.001** | 2.71 | 0.71-10.36 | 0.146 |
| Pretreatment Hb levels (anemia vs normal) | 2.03 | 1.01-4.12 | **0.049** | 1.87 | 0.67- 5.28 | 0.234 |

invasion, and lymphovascular space invasion (Table 2).

## Discussion

Anemia is frequently observed in cancer patients at the time of diagnosis with a prevalence of 30% to 90%, depending on the type of cancer. Gynecological malignancies are among the tumors characterized by a higher prevalence of anemia at diagnosis. According to the European Cancer Anemia Survey (ECAS), the Australian Cancer Anemia Survey (ACAS), and our 6-month survey; the percentage of patients with gynecologic malignancy who had anemia at enrollment were 49.1%, 65%, and 66%, respectively (Ludwig et al., 2004; Seshadri et al., 2005, Achariyapota et al., 2010). Our data also show a high prevalence of anemia in patients with endometrial cancer before surgery (39%).

Besides the negative effect on QoL, the presence of anemia itself has been found to be an unfavorable prognostic factor in a number of malignancies, including carcinoma of cervix (Gucer et al., 1998; Mundt et al., 1998; Logsdon et al., 1999), ovary (Obermair et al., 1998; Obermair et al., 2000; Munstedt et al., 2003; Gadducci et al., 2005; Di Maio et al., 2006; Eichbaum et al., 2009; Pongsanon et al., 2011). However, only few data are currently available concerning the correlation between anemia and prognostic factors in endometrial cancer. In the first retrospective study by Tamussino et al. 18% of 212 patients with endometrial cancer had Hb level <12 g/dL in blood samples drawn prior to surgery. Anemia was strongly associated with other unfavorable prognostic factors and was found to be related to an impaired overall survival at univariate but not at multivariate analysis (Tamussino et al., 2001). In 2009, Metindir et al. studied retrospectively 61 endometrial cancer patients who underwent surgical treatment consisting of total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, pelvic and para-aortic lymph node dissection, and peritoneal cytology. The author demonstrated that decreasing preoperative Hb levels reflected poor prognostic factors such as positive cytology and cervical involvement (Metindir et al., 2009). Our present data confirm the previous studies involving patients with endometrial cancer that anemia prior to surgery is associated with other poor prognostic factors and may have prognostic impact on disease-free survival and overall survival.

The etiology of cancer-related anemia is multifactorial, possibly associated with nutritional deficiencies, bleeding from tumor sites, bone marrow infiltration by the tumor, and the myelosuppressive effects of anticancer therapies. Although abnormal vaginal bleeding is the most common presenting symptom in patients with endometrial cancer, it is rarely severe enough to cause anemia. The basis for the association between low pretreatment Hb level and treatment outcome is complex and influenced by many factors. Tumor cells are known to produce and secrete several soluble cytokines (such as interleukin-1, interferon-gamma, and tumor necrosis factor) that may be able to decrease Hb levels by hemolysis, suppression of erythropoiesis, and impairment of erythropoietin response of erythroid medullary precursors. According to this hypothesis, anemia should be regarded as a paraneoplastic syndrome, a phenomenon of the biologic aggressiveness of cancer (Mercadante et al., 2000; Bron et al., 2001; Tas et al., 2002; Dicato, 2003; Weiss et al., 2005). An alternative hypothesis to explain the prognostic role of anemia is tumor hypoxia. Low Hb levels result in decreased oxygen transport capacity which causes decreased tumor oxygenation (Vaupel et al., 2003; Boogaerts et al., 2005). The effects of oxygenation on tumor biology have been long investigated. Höckel et al. measured tumor oxygenation using pO2 polarography and found that pO2 was a useful prognostic factor in patients with advanced-stage cancer of the uterine cervix (Hockel et al., 1996). Emerging evidence indicates that a hypoxic microenvironment can have a major influence on the malignant phenotype of the tumor and that oxygen may play an important role in the response to cancer treatment (Young et al., 1988; Graeber et al., 1996; Reynolds et al., 1996; Hockel et al., 2001; Vaupel et al., 2003; Van Belle et al., 2003). Previous studies involving patients with cancer have shown that non-anemic tumors are more responsive to adjuvant therapy. Both radiotherapy and chemotherapy were reported to be more effective in well oxygenated than in hypoxic conditions (Dische, 1991; Hockel et al., 1996; Liang, 1996; Eisenhauer et al., 1997; Thews et al., 1998). This could be another reason why anemic cancer patients have poor survival rates. Based on a systemic review of 19 observational studies of patients with cancer, all but one of these studies showed an association between anemia and decreased survival (Knight et al., 2004).

In conclusion, this study confirms that low pretreatment Hb level is associated with other unfavorable prognostic

factors in patients with endometrial cancer. In term of disease-free survival, the presence of anemia is proved to be a prognostic factor in the univariate but not the multivariate analyses.

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## References

Achariyapota V, Benjapibal M, Chaopotong P (2010). Prevalence and incidence of anemia in Thai patients with gynecologic cancer. *Asian Pacific J Cancer Prev*, **11**, 1229-33.

Alici S, Kaya S, Izmirli M, et al (2006). Analysis of survival factors in patients with advanced-stage gastric adenocarcinoma. *Med Sci Monit*, **12**, 221-9.

Boogaerts M, Mittelman M, Vaupel P (2005). Beyond anaemia management: evolving role of erythropoietin therapy in neurological disorders, multiple myeloma and tumour hypoxia models. *Oncology*, **69**, 22-30.

Bron D, Meuleman N, Mascaux C (2001). Biological basis of anemia. *Semin Oncol*, **28**, 1-6.

Caro JJ, Salas M, Ward A, et al (2001). Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*, **91**, 2214-21.

Di Maio M, Pisano C, Tambaro R, et al (2006). The prognostic role of pre-chemotherapy hemoglobin level in patients with ovarian cancer. *Front Biosci*, **11**, 1585-90.

Dicato M (2003). Anemia in cancer: some pathophysiological aspects. *Oncologist*, **8**, 19-21.

Dische S (1991). Radiotherapy and anaemia-the clinical experience. *Radiother Oncol*, **20**, 35-40.

Eichbaum MH, Weiss LM, Bruckner T, et al (2009). Prognostic impact of hemoglobin levels before and during carboplatin/taxane-based chemotherapy in patients with primary invasive epithelial ovarian cancer. *Med Sci Monit*, **15**, 156-63.

Eisenhauer EA, Vermorken JB, van Glabbeke M (1997). Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients. *Ann Oncol*, **8**, 963-8.

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.

Gadducci A, Sartori E, Landoni F, et al (2005). Pre-chemotherapy hemoglobin levels and survival in patients with advanced epithelial ovarian cancer who received a first-line taxane/platinum-based regimen: results of a multicenter retrospective Italian study. *Gynecol Oncol*, **98**, 118-23.

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

Graeber TG, Osmanian C, Jacks T, et al (1996). Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. *Nature*, **379**, 88-91.

Hockel M, Vaupel P (2001). Biological consequences of tumor hypoxia. *Semin Oncol*, **28**, 36-41.

Hockel M, Schlenger K, Aral B, et al (1996). Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. *Cancer Res*, **56**, 4509-15.

Knight K, Wade S, Balducci L (2004). Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med*, **116**, 11-26.

Ludwig H, Van Belle S, Barrett-Lee P, et al (2004). The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer*, **40**, 2293-306.

Liang BC (1996). Effects of hypoxia on drug resistance phenotype and genotype in human glioma cell lines. *J Neurooncol*, **29**, 149-55.

Logsdon MD, Eifel PJ (1999). FIGO stage IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. *Int J Radiat Oncol Biol Phys*, **43**, 763-75.

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

Munstedt K, Kovacic M, Zygmunt M, et al (2003). Impact of hemoglobin levels before and during chemotherapy on survival of patients with ovarian cancer. *Int J Oncol*, **23**, 837-43.

Mercadante S, Gebbia V, Marrazzo A, et al (2000). Anaemia in cancer: pathophysiology and treatment. *Cancer Treat Rev*, **26**, 303-11.

Mundt AJ, Connell PP, Campbell T, et al (1998). Race and clinical outcome in patients with carcinoma of the uterine cervix treated with radiation therapy. *Gynecol Oncol*, **71**, 1511-5.

Obermair A, Petru E, Windbichler G, et al (2000). Significance of pretreatment serum hemoglobin and survival in epithelial ovarian cancer. *Oncol Rep*, **7**, 639-44.

Obermair A, Handisurya A, Kaider A, et al (1998). The relationship of pretreatment serum hemoglobin level to the survival of epithelial ovarian carcinoma patients: a prospective review. *Cancer*, **83**, 726-31.

Pongsanon K, Benjapibal M, Ruengkhachorn I (2011). Prognostic significance of hemoglobin levels in patients with primary epithelial ovarian carcinoma undergoing platinum-based chemotherapy. *Asian Pacific J Cancer Prev*, **12**, 131-6.

Reynolds TY, Rockwell S, Glazer PM (1996). Genetic instability induced by the tumor microenvironment. *Cancer Res*, **56**, 5754-7.

Seshadri T, Prince HM, Bell DR, et al (2005). The Australian cancer anaemia survey: a snapshot of anaemia in adult patients with cancer. *Med J Aust*, **182**, 453-7.

Tas F, Eralp Y, Basaran M, et al (2002). Anemia in oncology practice: relation to diseases and their therapies. *Am J Clin Oncol*, **25**, 371-9.

Tamussino KF, Gücer F, Reich O, et al (2001). Pretreatment hemoglobin, platelet count, and prognosis in endometrial carcinoma. *Int J Gynecol Cancer*, **11**, 236-40.

Thews O, Koenig R, Kelleher DK, et al (1998). Enhanced radiosensitivity in experimental tumours following erythropoietin treatment of chemotherapy-induced anaemia. *Br J Cancer*, **78**, 752-6.

Van Belle SJ, Cocquyt V (2003). Impact of haemoglobin levels on the outcome of cancers treated with chemotherapy. *Crit Rev Oncol Hematol*, **47**, 1-11.

Vaupel P, Mayer A, Briest S, et al (2003). Hockel M: Oxygenation gain factor: a novel parameter characterizing the association between hemoglobin level and the oxygenation status of breast cancers. *Cancer Res*, **63**, 7634-7.

Weiss G, Goodnough LT (2005). Anemia of chronic disease. *N Engl J Med*, **352**, 1011-23.

Young SD, Marshall RS, Hill RP (1988). Hypoxia induces DNA overreplication and enhances metastatic potential of murine tumor cells. *Proc Natl Acad Sci USA*, **85**, 9533-7.