

An association between preoperative anemia and poor prognostic factors and decreased survival in early stage cervical cancer patients

Soyi Lim, Chae-Min Lee, Jong-Min Park, Sun-Young Jung, Kwang-Beom Lee

Department of Obstetrics and Gynecology, Gachon University Gil Medical Center, Incheon, Korea

Objective

To evaluate correlation of preoperative anemia with clinical outcomes in patients with early stage cervical cancer who were treated with radical hysterectomy and lymph node dissection.

Methods

Patients who underwent radical hysterectomy and lymph node dissection for cervical cancer from January 2001 to February 2012 were included in this study. Clinicopathological factors included in univariate and multivariate analysis were age, tumor histology, FIGO (International Federation of Gynecology and Obstetrics) stage, preoperative hemoglobin, depth of invasion, tumor size, parametrial involvement, resection margin, and lymph node status.

Results

A total of 387 patients were retrospectively analyzed in this study; 141 patients (36.4%) had preoperative anemia (hemoglobin <12 g/dL) and 16 out of 141 patients (11.3%) received blood transfusion for correction of preoperative anemia. Patients with preoperative anemia showed significant association with age <50 years, more advanced stage, non-squamous cell carcinoma histology, larger tumor size, deeper stromal invasion, and lymph node metastasis ($P<0.05$). Both relapse-free survival and overall survival were worse in patients with preoperative anemia in univariate analysis. In multivariate analysis, overall survival was worse in patients with preoperative anemia, but relapse-free survival was not associated with preoperative anemia. In the intergroup analysis of anemic patients for the effect of preoperative blood transfusion, preoperative anemia correction did not affect survival.

Conclusion

Preoperative anemia was not an independent prognostic factor for survival in patients with early cervical cancer. However, it was associated with poor prognostic factors. Further study in large population is needed.

Keywords: Anemia; Hysterectomy; Uterine cervical neoplasms

Introduction

Pretreatment hemoglobin (Hb) level is a well-known prognostic factor in patients with advanced cervical cancer [1,2], endometrial cancer [3], and ovarian cancer [4,5]. The relationship between anemia and poor treatment outcomes has been studied by many investigators. However, the correct underlying mechanisms are complex and remain unknown. Tumor hypoxia has been thought to cause tumor growth and resistance to therapy as it is associated with angiogenesis, genetic mutations, resistance to apoptosis, and resistance to free radicals resulting from chemotherapy and radiotherapy [6]. Therefore,

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Corresponding author: Kwang-Beom Lee

Department of Obstetrics and Gynecology, Gachon University Gil Medical Center, 21 Namdong-daero 774beon-gil, Namdong-gu, Incheon 405-760, Korea

Tel: +82-32-460-3254 Fax: +82-32-460-3290

E-mail: leekwbm@gilhospital.com

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many attempts have been made to correct anemia either with a blood transfusion or erythropoiesis-stimulating agents, however, the clinical benefit remains elusive [7,8].

In the setting of advanced cervical cancer undergoing radiotherapy, a number of studies have suggested that anemia at presentation and/or during treatment might heavily impair prognosis [1,2,9]. This may be explained by the fact that tissue hypoxia mediates resistance to radiation. Alternatively, the possibility that anemia might also characterize biologically more aggressive tumors cannot be excluded [9,10]. Therefore, it has been proposed that low Hb levels could be a useful parameter for prediction of poor response and unfavorable clinical outcome in patients undergoing radiotherapy or concurrent chemoradiation [4,11]. However, most studies on association of cervical cancer and anemia have included patients with locally advanced cervical cancer treated with radiotherapy or concurrent chemoradiation. In the current study, we hypothesized that anemic patients with early stage cervical cancer may have subclinical hypoxemia; therefore, clinical outcomes may be worse for anemic patients, even those who underwent radical surgery in the early stage of cervical cancer.

This retrospective study was conducted in order to evaluate whether preoperative anemia and preoperative anemia correction by blood transfusion might affect clinical outcomes in surgically treated early stage cervical cancer.

Materials and methods

A total of 387 patients underwent surgery for cervical cancer in our department between January 2001 and February 2012. We identified patients with cervical cancer stage IB to IIA who underwent type III radical hysterectomy with pelvic and/or paraaortic lymph node dissection. After approval of the institutional review board of our institution, data were collected retrospectively and patients' age, tumor histologic subtype, stage according to the International Federation of Gynecology and Obstetrics (FIGO), histopathologic features, the first pretreatment automated blood count within two weeks before surgery, preoperative anemia correction by blood transfusion, modalities of adjuvant treatment, recurrence, and survival were reviewed from the hospital charts and follow-up records. We excluded patients with stage IA, received neoadjuvant chemotherapy or preoperative radiotherapy, had known inflammatory conditions, had a history of other primary cancer, and had known coagulopathy or blood disorder. A blood count was performed

using an electronic particle counting device at least two weeks before the operation. A Hb <12 g/dL without acute blood loss was defined as pretreatment anemia [12].

Patients were evaluated by conventional workup, including medical history, pelvic examination, rectovaginal examination, chest radiography, and colonoscopy. Also, laboratory examinations, magnetic resonance imaging, and positron emission tomography/computed tomography were performed. All patients underwent type III radical hysterectomy and pelvic lymph node dissection with or without para-aortic lymph node dissection. Adjuvant treatments were performed according to intra-institutional guidelines.

Survival times were calculated from the date of surgery. A relapse was defined as radiographic or pathologic evidence of loco-regional tumor recurrence or distant metastasis at any time after initial treatment. Primary endpoints of the study were relapse-free survival (RFS) and overall survival (OS). Factors in the univariate and multivariate analysis included age, FIGO stage, tumor cell type, tumor diameter, lymphovascular

Table 1. Clinicopathological characteristics, demographics and preoperative hematological profiles (n=387)

Variable	Value
Age (yr, median)	46 (18–79)
FIGO stage	
IB1	284 (73.4)
IB2	70 (18.1)
IIA	33 (8.5)
Histology	
Squamous cell carcinoma	287 (74.2)
Adenocarcinoma	66 (17.0)
Adenosquamous cell carcinoma	32 (8.3)
Others	2 (0.5)
Adjuvant treatment	
No adjuvant treatment	130 (33.6)
Radiotherapy	28 (7.2)
Concurrent chemoradiation	118 (30.5)
Chemotherapy	111 (28.7)
Preoperative blood transfusion	
No	371 (95.9)
Yes	16 (4.1)
Hemoglobin count (g/dL)	12.2±1.5
Anemia (no. of cases)	141 (36.4)

Values are presented as number (%) or mean±standard deviation. FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Distribution of preoperative Hb status according to clinico-pathological variables (n=387)

Characteristics	No. of patients	Cases without anemia (Hb ≥12 g/dL)	Cases with anemia (Hb <12 g/dL)	P-value
Age (yr)				
<50	250	144 (57.6)	106 (42.4)	0.001
≥50	137	102 (74.5)	35 (25.5)	
FIGO stage				
IB1	284	197 (69.4)	87 (30.6)	<0.001
IB2	70	30 (42.9)	40 (57.1)	
IIA	33	19 (57.6)	14 (42.4)	
Histology				
SCC	287	191 (66.6)	96 (33.4)	0.039
Non-SCC	100	55 (55.0)	45 (45.0)	
Tumor diameter (cm)				
≤4	279	193 (69.2)	86 (30.8)	<0.001
>4	108	53 (49.1)	55 (50.9)	
Lymphovascular space invasion				
No	191	127 (66.5)	64 (33.5)	0.238
Yes	196	119 (60.7)	77 (39.3)	
Depth of invasion				
≤2/3	202	143 (70.8)	59 (29.2)	0.002
>2/3	185	103 (55.7)	82 (44.3)	
Lymph node metastasis				
No	298	198 (66.4)	100 (33.6)	0.031
Yes	89	48 (53.9)	41(46.1)	
Resection margin				
No	368	236 (64.1)	132 (35.9)	0.310
Yes	19	10 (52.6)	9 (47.4)	
Parametrial involvement				
No	319	205 (64.3)	114 (35.7)	0.537
Yes	68	41 (60.3)	27 (39.7)	

Values are presented as number or number (%).

Hb, hemoglobin; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma.

space invasion, depth of stromal invasion, lymph node metastasis, resection margin status, parametrial involvement, preoperative anemia, and correction of anemia by blood transfusion. The Kaplan-Meier method and the log-rank test were used to estimate the OS and recurrence-free survival. For patients who remained alive, data were censored at the date of the last contact. Multivariate analysis was performed using Cox proportional hazard analysis with the forward conditional method. Association between pretreatment Hb and each variable was examined by chi-square test. All statistical analyses

were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). *P*-value <0.05 was considered statistically significant.

Results

A total of 387 patients were retrospectively analyzed in this study. A summary of patient characteristics is shown in Table 1. Median follow-up period was 40 months (range, 1–125 months), and the median age was 46 years (range, 18–79

Table 3. Survivals based on preoperative anemia and preoperative blood transfusion

	n	5-Year RFS (%)	P-value	5-Year OS (%)	P-value
All patients (n=387)					
Hb <12 g/dL	141	76.0	0.027	90.9	0.002
Hb ≥12 g/dL	246	84.3		97.8	
Anemic patients (n=141)					
Transfusion	16	85.1	0.460	100	0.264
No transfusion	125	74.8	-	89.8	

RFS, relapse-free survival; OS, overall survival; Hb, hemoglobin.

Table 4. Factors associated with survival in multivariate analysis

	Hazard ratio	95% confidence interval	P-value
Relapse-free survival			
Parametrial involvement	4.332	2.451–7.659	<0.001
Lymph node metastasis	2.024	1.147–3.573	0.015
Non-squamous cell carcinoma histology	3.202	1.899–5.399	<0.001
Overall survival			
Preoperative anemia	4.954	1.358–18.077	0.015
Parametrial involvement	3.952	1.179–13.244	0.026
Lymph node metastasis	7.075	1.752–28.576	0.006

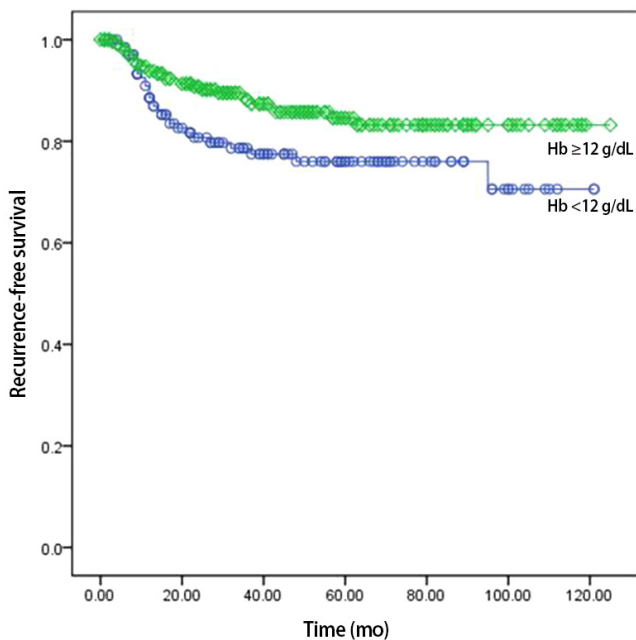


Fig. 1. Recurrence-free survival based on preoperative anemia ($P=0.027$). Hb, hemoglobin.

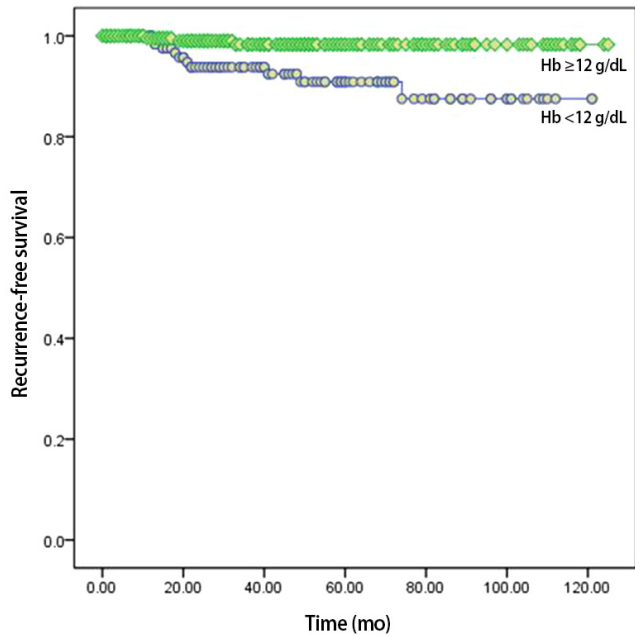


Fig. 2. Overall survival based on preoperative anemia ($P=0.002$). Hb, hemoglobin.

years). The majority of patients ($n=284$, 73.4%) had stage IB1 disease. For the entire cohort, the five-year FRS and OS were

81.5 and 95.5%, respectively. Median survival for the entire cohort has not been reached. There were 141 patients (36.4%)

who had preoperative anemia (Hb <12 g/dL) and 16 out of 141 patients (11.3%) received blood transfusion for correction of preoperative anemia.

These 141 patients with preoperative anemia showed significant association with age <50 years ($P=0.001$), more advanced stage ($P=0.003$), non-squamous cell carcinoma (SCC) histology ($P=0.035$), larger tumor size ($P<0.001$), deeper stromal invasion ($P=0.002$), and lymph node metastasis ($P=0.031$). Lymphovascular space involvement, resection margin status, and parametrial involvement did not show a significant association with preoperative anemia (Table 2).

In univariate analysis, the factors associated with poorer RFS were FIGO stage, non-SCC histology, larger tumor diameter, positive lymphovascular space invasion, deeper stromal invasion, lymph node metastasis, positive resection margin, parametrial involvement, and preoperative anemia. In addition, factors associated with poorer OS were FIGO stage, tumor diameter, lymphovascular space invasion, depth of invasion, lymph node metastasis, positive resection margin, parametrial involvement, and preoperative anemia. In the intergroup analysis in anemic patients, correction of preoperative anemia by blood transfusion did not affect either RFS or OS (Table 3). Preoperative leukocytosis and thrombocytosis did not affect survival outcomes.

In univariate analysis, when considering OS and RFS, a significant difference was observed in subgroups of patients with a lower level of Hb. RFS was worse in patients with Hb <12 g/dL versus Hb \geq 12 g/dL ($P=0.027$) (Fig. 1). OS was also worse in patients with Hb <12 g/dL versus Hb \geq 12 g/dL ($P=0.002$) (Fig. 2).

In multivariate analysis including the following factors: age, stage, histologic subtype, tumor diameter, lymphovascular space invasion, depth of stromal invasion, lymph node metastasis, resection margin status, parametrial involvement, preoperative anemia, and correction of preoperative anemia by blood transfusion using conditional forward Cox proportional hazard analysis, indicators of RFS were parametrial involvement, lymph node metastasis, and histologic subtype of non-SCC. Regarding OS, preoperative anemia <12 g/dL, parametrial involvement, and lymph node metastasis were independent indicators (Table 4).

Discussion

Findings of this study showed an association of low preoperative Hb levels with poor prognostic factors and less favor-

able clinical outcomes in early stage cervical cancer patients undergoing radical hysterectomy and lymph node dissection. Multivariate analysis showed that preoperative anemia had an impact on OS and that preoperative transfusion had no effect on survival. However, decreased RFS was associated with anemia in univariate analysis, there was no statistical significance in multivariate analysis. A number of previously reported studies have suggested that anemia at presentation and/or during treatment might heavily impair prognosis in cervical cancer patients undergoing radiotherapy [13-15]. It may represent a surrogate marker for tissue hypoxia, which mediates resistance to radiation. In addition, the possibility that anemia might also characterize biologically more aggressive tumors may be considered [9,10].

Although an association of anemia with prognosis in patients with cervical cancer has been reported [1,2,13-15], most studies have included patients with locally advanced cervical cancer treated with radiotherapy or concurrent chemoradiation. Few studies have reported on the influence of pretreatment of anemia on clinical outcomes in patients with early stage cervical cancer undergoing surgical treatment. In various solid tumors, the significance of preoperative anemia has been demonstrated in patients who underwent surgical treatment. In studies on patients with non-small cell lung cancer who were treated with surgery, preoperative anemia was reported as an independent negative prognostic factor [16,17].

In addition, one study reported that low pre-treatment Hb level may reflect poor prognostic factors such as positive cytology and cervical involvement in patients with endometrial cancer [18]. Our results support the association of preoperative Hb with such poor pathological variables and survival. In the current study, preoperative anemia showed an association with FIGO stage IB2, non-squamous cell histology, larger tumor diameter, deeper invasion depth, and lymph node metastasis. The results of this study appear to indicate that anemia may be a prognostic factor even for early stage cervical cancer patients.

Anemia is prevalent in the general population and is more common among cancer patients; 27% to 50% of patients undergoing cancer treatment are estimated as having baseline anemia [19,20]. Intratumoral bleeding from a friable tumor surface can result in substantial blood loss, and, therefore, anemia may be commonly seen in cervical cancer. Approximately 30% of patients with cervical cancer present with anemia before treatment [21]. In the current study, 141 out of 387 patients (36.4%) had preoperative anemia (Hb <12 g/dL).

However, the pathophysiology of anemia and its relation to poorer outcomes in cancer patients remains controversial. The presence of anemia itself may be related to aggressive tumor behavior and poor prognosis by exacerbating tumor hypoxia [9,10,22]. Several biological factors can explain how anemia can lead to poor outcomes. Evidence from studies on cancer of the lung [16,17], head and neck [12], and ovarian cancer [4] has demonstrated the adverse prognostic impact of tumor hypoxia within the tumor bed, structural and functional abnormalities result in haphazard architecture hindering oxygen diffusion from vessels to individual cells and causing hypoxia. Low oxygen tension within cancer cells initiates biological behaviors that lead to formation of a more aggressive phenotype and induction of angiogenesis. High levels of circulating angiogenic factors have also been reported in patients with anemia. Lack of oxygen within tissue hinders generation of free radicals, hence, resulting in resistance to treatment. Tumor hypoxia also appears to diminish the efficacy of certain chemo- and immune-therapeutic dependence on normal local oxygen levels [23]. Therefore, anemia and hypoxia mainly impact local control and can affect survival [24]. However, in the current study, preoperative anemia showed independent association with OS. RFS showed an association with preoperative anemia in univariate analysis and did not show an association in multivariate analysis. The difference between our study and previous studies is that our study only included patients with early stage cervical cancer who underwent radical hysterectomy.

Correction of anemia via transfusion or administration of recombinant human erythropoietin has been suggested to improve local control and OS in patients with solid tumors, however, the clinical benefit remains elusive [8]. If correction of anemia does not result in improved outcomes and not all tumors are associated with anemia, it is possible that tumors associated with anemia are more aggressive, and destined to poorer outcomes. Tumors can be heterogenous and exhibit unpredictable clinical behavior, even for the same histology and stage. One study reported that biologically aggressive tumors may release various cytokines, resulting in anemia, cachexia, and other systemic effects [25]. Therefore, anemia could be viewed as a marker of high-risk disease.

In conclusion, our data suggest that preoperative anemia was associated with poor prognostic factors in patients with early cervical cancer who underwent radical hysterectomy and lymph node dissection. Preoperative anemia was associated with OS, but RFS did not show significant association. Therefore preoperative anemia was not a significant prognostic

factor in patients with early stage cervical cancer. Although, preoperative anemia is not an independent prognostic factor, it may be associated with poor prognostic factors in patients with early stage cervical cancer. In the current study, correction of anemia with transfusion in the preoperative setting did not affect the clinical outcomes. And anemia may be a sign of a more aggressive tumor that is at an increased risk of poor survival. More research into the opinion regarding adjuvant therapy in early-stage cervical cancer patients with anemia is needed.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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