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Impact of preoperative leukocyte alteration in surgically-treated early-stage cervical cancer patients with low-risk, intermediate-risk or high-risk factors

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Summary

Purpose: The aim of this study was to investigate the prognostic impact of a preoperative leukocyte alteration in patients with surgically-treated early-stage cervical cancer. *Materials and Methods:* The baseline characteristics and outcome data of early-stage cervical cancer patients who were treated with radical hysterectomy between 1996 and 2011 were collected and retrospectively reviewed. The patients were separated into three risk groups (low-risk, intermediate-risk, and high-risk) according to the pathological risk factors exhibited by their tumors. A Cox proportional hazards regression model was used to investigate the prognostic significance of a preoperative leukocytosis (≥ 10,000 μ/l). *Results:* A preoperative leukocytosis was observed in 0.9%, 6.6%, and 8.6% of the patients in the low-risk, intermediate-risk, and high-risk groups, respectively. In multivariate analysis, a preoperative leukocytosis was found to be an independent prognostic factor in intermediate-risk or high-risk groups. *Conclusion:* The preoperative leukocytosis is an independent predicator of shorter progression-free survival (PFS) in surgically-treated early-stage cervical cancer patients, especially those with intermediate-risk or high-risk factors.

Key words: Leukocytosis; Cervical cancer; Radical surgery; Survival.

Introduction

Early-stage cervical cancer can be treated with radical hysterectomy or definitive radiotherapy, which produces similar survival outcomes [1-5]. Risk factors that compromise the treatment outcomes of early-stage cervical cancer patients who are primarily treated with radical surgery have been identified in previous studies [6-8]. Generally, patients with risk factors such as positive pelvic nodes, parametrial invasion, or a positive surgical margin are regarded as being at high risk of recurrence (the high-risk group). Moreover, patients with tumors that are confined to the cervix who display risk factors such as a large tumor, lymphovascular space involvement (LVSI), or deep stromal invasion (DSI) are considered to be at intermediate risk of recurrence (the intermediate-risk group) [6-8]. Patients in the intermediate-risk or high-risk group are recommended to receive adjuvant radiotherapy following radical hysterectomy. A Gynecologic Oncology Group phase III study (GOG 109/SWOG 8797) demonstrated that the addition of cisplatin-based concurrent chemoradiotherapy (CCRT) to postoperative radiotherapy improved survival in patients with high-risk factors [9]. With regards to intermediate-risk patients, another GOG phase III study (GOG 92) reported that adjuvant radiotherapy significantly reduced the risk of recurrence and prolonged progression-free survival (PFS) [10, 11]. Although retrospective studies have suggested the superiority of adjuvant CCRT compared with pelvic radiotherapy in intermediate-risk patients, no randomized prospective trials comparing postoperative CCRT with radiotherapy alone in this patient population have been completed [12-14]. Currently, a prospective randomized study (GOG 0263) is investigating the role of CCRT in intermediate-risk cervical cancer patients with regards to its effects on quality of life, long-term complications, and survival outcomes [15].

Identifying new prognostic factors for cervical cancer would improve our understanding of cervical cancer biology, help to stratify patients into risk groups, select patients that require postoperative adjuvant radiotherapy, and identify those who are highly likely to develop recurrence after the standard initial treatment. Tumor-related leukocytosis (TRL) is a paraneoplastic syndrome that is occasionally encountered in patients with malignant tumors, either at the initial diagnosis or during the course of the disease [16]. The present authors have recently reported that TRL is associated with a poor prognosis in patients with newly diagnosed cervical cancer and recurrent cervical cancer [17, 18]. In the analyses of the significance of TRL in cervical cancer patients according to the type of treatments, TRL is

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associated with a poor prognosis in patients that are treated with definitive radiotherapy or platinum-based chemotherapy [19,20]. However, as most of the patients included in the aforementioned studies had FIGO Stage III-IV or recurrent diseases, the significance of TRL in early-stage cervical cancer patients remains unclear [19, 20]. Moreover, the prognostic significance of TRL in surgically-treated cervical cancer patients remains to be elucidated.

In the current study, the authors retrospectively investigated the incidence and prognostic significance of preoperative leukocytosis in early-stage cervical cancer patients that were treated with radical hysterectomy.

Materials and Methods

Permission to proceed with the data acquisition and analysis was obtained from the institutional review board of Osaka University Hospital. A list of patients who had undergone radical hysterectomy and pelvic lymphadenectomy for FIGO stage IA2-IIB cervical cancer between January 1996 and December 2011 was generated from the institutional tumor registries. Then, their clinical data were retrospectively reviewed through a chart review. Of the 394 patients included in the current study, 330 had been examined in previous clinical studies [21-23].

At this institution, the histological classification of cervical cancer is performed by two pathologists based on the criteria outlined by the World Health Organization (WHO) for tumors of the uterine cervix. The patients were clinically staged according to the International Federation of Gynecology and Obstetrics staging criteria without general anesthesia. The pretreatment work-up consisted of a complete medical history, a physical examination, a complete blood count, biochemistry panels, chest X-rays, CT scans of the abdomen and pelvis, MRI, and optional intravenous pyelography, cystoscopy, and rectosigmoidoscopy. In all patients, a preoperative para-aortic lymph node (PALN) evaluation was conducted by performing a CT scan of the abdomen as part of the initial evaluation.

All patients were treated with radical hysterectomy (type III) and pelvic lymphadenectomy, as reported previously [21, 23]. The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, suprainguinal, and presacral lymph nodes. An intraoperative assessment of the PALN was routinely performed by palpation. When PALN metastasis was suspected on a preoperative CT scan or during intraoperative palpation, a biopsy was performed for confirmation. Patients who had biopsy-confirmed PALN metastasis were excluded from the study.

Postoperative radiotherapy is indicated when a patient's pathological report displays any one of the following 'high-risk' prognostic factors: parametrial invasion, pelvic lymph node metastasis, or a positive surgical margin, or one of the following 'intermediate-risk' prognostic factors: DSI, LVSI, or a large tumor (over 4 cm in diameter).

Basically, the patients were treated with external beam pelvic radiotherapy plus concurrent chemotherapy, as reported previously [22-27]. Patients who refused CCRT or who developed cervical cancer before the introduction of CCRT were treated with pelvic radiotherapy alone. Postoperative pelvic radiotherapy was performed using 10 megavolt (MV) X-rays delivered from a linear accelerator using the anteroposterior parallel opposing technique. The superior margin of the external radiation field was located at the top of the fifth lumber vertebra, and the inferior border of the obturator foramen was used as the inferior margin. Laterally, the field extended 2 cm beyond the lateral margin of the bony pelvic wall. The authors used multi-leaf collimators to block the upper and lower corners of the radiation field. External irradiation was delivered to the whole pelvis at 2 Gy per fraction in five fractions per week for a total of 25 fractions (50 Gy).

At this institutions, nedaplatin is employed as a radiosensitizing agent for patients with cervical cancer. Nedaplatin was administered intravenously during the course of pelvic radiotherapy, as reported previously [24-29].

Seven patients who refused postoperative radiotherapy with or without concurrent chemotherapy were treated with platinum-based combination chemotherapies (carboplatin plus paclitaxel in six patients and carboplatin, paclitaxel, and epirubicin in one patient). The patients were followed-up regularly by both gynecological oncologists and radiation oncologists, as reported previously [29, 30]. When recurrence was suspected, a biopsy sample was obtained for confirmation whenever possible.

During the period between the initial diagnosis and the initial surgical procedure, all patients underwent at least two blood tests including a complete blood count, and the lowest leukocyte count obtained during these tests were employed in the current analyses. Preoperative leukocytosis was defined as the detection of persistent leukocyte count exceeding 10,000/μl, on at least two separate occasions. Patients who were administered corticosteroids or were suffering from acute or chronic infections were excluded. No HIV-infected patients were included in the current study.

Continuous data were compared between the groups using the Student's *t*-test, Wilcoxon rank-sum test, or median test, as appropriate. Frequency counts and proportions were compared between the groups using the chi-square test or two-tailed Fisher's exact test, as appropriate. The authors performed univariate analyses by comparing the Kaplan–Meier curves for each subgroup using the log-rank test. PFS was defined as the time from the date of the primary surgery to the date of the first physical or radiographic evidence of disease progression. Cox proportional hazards regression analysis was performed to identify independent predictors of survival. *P*-values of < 0.05 were considered to be statistically significant. All analyses were carried out using the software JMP, version 11.0.

Results

A total of 394 consecutive patients with cervical cancer were included in this retrospective study. The clinicopathological characteristics of these patients are summarized in Table 1. The patients' median age was 48 years. Of the 394 patients, 208 had Stage IA2-IB1, 104 had Stage IB2-IIA, and 82 had Stage IIB disease. Histologically, 247 patients (62.7%) had squamous cell carcinoma, and 147 (37.3%) displayed non-squamous histology. Seventy-nine patients had tumors with a maximum tumor diameter of $\geq$ 40 mm. Of the 394 patients, 256 received postoperative adjuvant therapy (radiotherapy in 249 cases and chemotherapy in seven cases) because their cervical tumors displayed intermediate-risk or high-risk pathological factors.

Of a total of 394 patients, preoperative leukocytosis was observed in 22 patients (5.6%). The preoperative white blood cell (WBC) counts of these patients ranged from 10,130 to 19,850/μl. As shown in Table 1, the patients with

Table 1. — *Comparison of clinicopathological features between patients with leukocytosis and those without leukocytosis.*

		All patients (%) n=394	Patients with leukocytosis (%) n=22	Patients without leukocytosis (%) n=372	*p*-value
Age (years)	Mean	48.1	46.4	48.3	0.44
	≤ 50	229 (58.1)	15 (68.2)	214 (57.5)	0.56
	51-74	163 (41.4)	7 (31.8)	156 (41.9)	
	≥ 75	2 (0.5)	0 (0)	2 (0.5)	
FIGO Stage	lA2-lB1	208 (52.8)	6 (27.3)	202 (54.3)	0.02
	lB2-llA	104 (26.4)	7 (31.8)	97 (26.1)	
	llB	82 (20.8)	9 (40.9)	73 (19.6)	
Histology	SCC	247 (62.7)	16 (72.7)	231 (62.1)	0.31
	Non-SCC	147 (37.3)	6 (27.3)	141 (37.9)	
Tumor size (mm)	< 40	315 (80.0)	10 (45.5)	305 (82.0)	<0.0001
	≥ 40	79 (20.0)	12 (54.4)	67 (18.0)	
LVSI	No	158 (40.1)	5 (27.7)	153 (41.1)	0.08
	Yes	236 (59.9)	17 (72.3)	219 (58.9)	
DSI	No	172 (43.6)	4 (18.2)	168 (45.2)	0.01
	Yes	222 (56.4)	18 (81.8)	204 (54.8)	
Parametrial involvement	No	311 (78.9)	14 (63.6)	297 (79.8)	0.07
	Yes	83 (21.1)	8 (36.4)	75 (20.2)	
Lymph node metastasis	No	288 (73.2)	14 (63.6)	274 (73.7)	0.30
	Yes	106 (26.9)	8 (36.4)	98 (26.3)	
Margin status	Negative	386 (98.0)	20 (90.9)	366 (98.4)	0.07
	Positive	8 (2.0)	2 (9.1)	6 (1.6)	

FIGO: International Federation of Gynecology and Obstetrics; SCC: squamous cell carcinoma; LVSI: lymphovascular space involvement; DSI: deep stromal invasion.

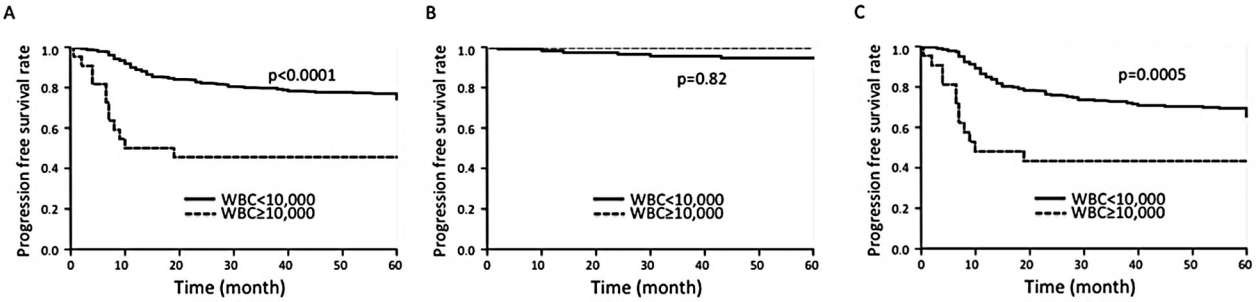

Figure 1. — Progression-free survival among patients with and without leukocytosis.
A) All patients. Progression-free survival was significantly shorter among the patients with leukocytosis (log-rank, $p < 0.0001$). B) Patients in low-risk group. Progression-free survival was similar between the two groups (log-rank; $p = 0.82$). C) Patients in intermediate-risk or high-risk group. Progression-free survival was significantly shorter among the patients with leukocytosis (log-rank; $p = 0.0005$).

preoperative leukocytosis (≥ 10,000/μl) presented with larger tumors ($p < 0.0001$) and deeper stromal invasion ($p = 0.01$) than the patients without preoperative leukocytosis. In addition, the patients with preoperative leukocytosis received postoperative adjuvant treatment more frequently than those without preoperative leukocytosis (90.9% *vs.* 63.4%, $p = 0.004$).

To investigate the prognostic significance of preoperative leukocytosis in surgically-treated early-stage cervical cancer patients, the authors first conducted univariate analyses. As shown in Table 2 and Figure 1A, in addition to conventional pathological risk factors including tumor size, LVSI, DSI, parametrial involvement, lymph node metastasis, and margin status, a preoperative leukocytosis was found to be correlated with shorter PFS in the univariate analyses. Conversely, the patients' histological diagnoses did not provide prognostic information. In the multivariate analyses, in addition to histology and the conventional pathological risk factors, a preoperative leukocytosis was also demonstrated to be an independent prognostic factor for survival (Table 2).

Among the 22 patients who developed preoperative leukocytosis, 20 had significantly elevated neutrophil counts (≥ 7,500/μl). When examined in more detail, it was found that 18 had neutrophilia alone, three had both neutrophilia and eosinophilia, and one patient had monocyto-

Table 2. — *Univariate and multivariate analysis of leukocytosis predictive of progression free survival.*

		Univariate analysis		Multivariate analysis	
Variables		Hazard ratio (95%Cl)	*p*-value	Hazard ratio (95%Cl)	*p*-value
WBC (μ/l)	< 10,000	1	0.0003	1	0.03
	≥ 10,000	3.68 (1.91-6.46)		2.18 (1.10-3.96)	
Age (years)	≤ 50	1	0.30		
	≥ 51	1.23 (0.83-1.80)			
Histology	SCC	1	0.13	1	0.0003
	Non-SCC	1.35 (0.91-1.99)		2.16 (1.43-3.25)	
Tumor size (mm)	< 40	1	<0.0001	1	0.0002
	≤ 40	4.64 (3.12-6.85)		2.31 (1.50-3.54)	
LVSI	No	1	<0.0001	1	0.005
	Yes	5.56 (3.23-10.4)		2.57 (1.34-5.26)	
DSI	No	1	<0.0001	1	0.049
	Yes	4.39 (2.70-7.53)		1.76 (1.00-3.23)	
Parametrial involvement	No	1	<0.0001	1	0.02
	Yes	4.00 (2.7-5.89)		1.68 (1.07-2.64)	
Lymph node metastasis	No	1	<0.0001	1	0.03
	Yes	3.80 (2.58-5.61)		1.62 (1.06-2.49)	
Margin status	Negative	1	0.003	1	<0.0001
	Positive	3.02 (1.52-5.39)		7.90 (3.19-17.7)	

WBC: white blood cells; SCC: squamous cell carcinoma; LVSI: lymphovascular space involvement; DSI: deep stromal invasion.

Table 3. — *Univariate and multivariate analysis of neutrophilia predictive of progression free survival.*

			Univariate analysis		Multivariate analysis	
Variables		n	Hazard ratio (95%Cl)	*p*-value	Hazard ratio (95%Cl)	*p*-value
Neutrophil (μ/l)	< 7,500	372	1	0.003	1	0.04
	≥ 7,500	22	3.02 (1.52-5.39)		2.08 (1.03-3.78)	
Age (years)	≤ 50	229	1	0.30		
	≥ 51	165	1.23 (0.83-1.80)			
Histology	SCC	247	1	0.13	1	0.0003
	Non-SCC	147	1.35 (0.91-1.99)		2.18 (1.44-3.28)	
Tumor size (mm)	< 40	315	1	<0.0001	1	<0.0001
	≥ 40	79	4.64 (3.12-6.85)		2.46 (1.60-3.76)	
LVSI	No	158	1	<0.0001	1	0.004
	Yes	236	5.56 (3.23-10.4)		2.54 (1.32-5.17)	
DSI	No	172	1	<0.0001	1	0.04
	Yes	222	4.39 (2.70-7.53)		1.78 (1.02-3.27)	
Parametrial involvement	No	311	1	<0.0001	1	0.03
	Yes	83	4.00 (2.7-5.89)		1.64 (1.04-2.56)	
Lymph node metastasis	No	288	1	<0.0001	1	0.02
	Yes	106	3.80 (2.58-5.61)		1.64 (1.08-2.53)	
Margin status	Negative	386	1	0.003	1	<0.0001
	Positive	8	3.02 (1.52-5.39)		7.83 (3.16-17.5)	

SCC: squamous cell carcinoma; LVSI: lymphovascular space involvement; DSI: deep stromal invasion.

sis. None of the patients had basophilia. Thus, the authors also determined the prognostic significance of preoperative neutrophilia (≥ 7,500/μl) in this patient population. In the multivariate analysis in which the WBC count was not included as a prognostic variable (Table 3), in addition to histology and the conventional pathological risk factors, a presence of preoperative neutrophilia (≥ 7,500/μl) was found to be a significant prognostic factor in terms of PFS (hazard ratio for death, 2.08; 95% confidence interval, 1.03 to 3.78; $p = 0.04$).

The authors next examined the prognostic significance of preoperative leukocytosis according to the patients' pathological risk factor classification. The preoperative leukocytosis was observed in one1 (0.9%), nine (6.6%), and 12 (8.6%) of the patients in the low-risk, intermediate-risk, and high-risk group, respectively. The only patient who displayed preoperative leukocytosis in the low-risk group was free of disease after a follow-up period of 60

Table 4. — *Univariate and multivariate analysis of leukocytosis predictive of progression free survival in patients with intermediate risk or high-risk prognostic factors.*

		Univariate analysis		Multivariate analysis	
Variables		Hazard ratio (95%Cl)	*p*-value	Hazard ratio (95%Cl)	*p*-value
WBC (μ/l)	< 10,000	1	0.003	1	0.02
	≥ 10,000	2.83 (1.46-4.98)		2.24 (1.13-4.07)	
Age (years)	≤ 50	1	0.62		
	≥ 51	1.10 (0.74-1.64)			
Histology	SCC	1	0.03	1	0.0006
	Non-SCC	1.57 (1.04-2.33)		2.14 (1.39-3.26)	
Tumor size (mm)	< 40	1	<0.0001	1	0.0002
	≥ 40	3.14 (2.10-4.69)		2.29 (1.49-3.51)	
LVSI	No	1	0.007	1	0.03
	Yes	2.51 (1.25-5.97)		2.22 (1.06-5.43)	
DSI	No	1	0.02	1	0.12
	Yes	1.98 (1.12-3.81)		1.62 (0.89-3.19)	
Parametrial involvement	No	1	<0.0001	1	0.02
	Yes	2.67 (1.79-3.97)		1.70 (1.08-2.65)	
Lymph node metastasis	No	1	<0.0001	1	0.03
	Yes	2.45 (1.64-3.67)		1.61 (1.05-2.48)	
Margin status	Negative	1	<0.0001	1	<0.0001
	Positive	13.9 (6.02-28.3)		7.84 (3.15-17.7)	

WBC: white blood cells; SCC: squamous cell carcinoma; LVSI: lymphovascular space involvement; DSI: deep stromal invasion.

Table 5. — *Positive predictive values and negative predictive values for recurrence.*

	Number of patients	Number of recurrence	Positive predictive value (%)	Negative predictive value (%)
WBC ≥ 10,000	22	12	54.55	75.27
Neu ≥ 7,500	22	11	50	75.00
Non-SCC histology	147	45	30.61	76.11
Tumor size ≥ 40 mm	79	46	58.23	81.59
LVSI	236	91	38.56	91.77
DSI	222	86	38.74	89.53
Parametrium invasion	83	47	56.63	81.67
Lymph node metastasis	106	55	51.89	82.99
Margin positive	8	8	100	75.13

WBC: white blood cells; Neu: neutrophils; LVSI: lymphovascular space involvement; DSI: deep stromal invasion.

months (Figure 1B). These results indicate that preoperative leukocytosis is more prognostically important in patients that display intermediate-risk or high-risk pathological factors. Thus, the authors further investigated the prognostic significance of preoperative leukocytosis in separate univariate and multivariate analyses in which only patients from the intermediate-risk or high-risk groups were included. As shown, preoperative leukocytosis was associated with shorter PFS in patients that displayed intermediate-risk or high-risk prognostic factors (Figure 1C). In the multivariate analyses, the presence of preoperative leukocytosis was found to be an independent prognostic factor in patients that display intermediate-risk or high-risk pathological factors (Table 4).

The authors finally evaluated the utility of preoperative leukocytosis for predicting the development of recurrence (Table 5). Twelve out of 22 patients with preoperative leukocytosis developed recurrent lesions. The positive predictive value of preoperative leukocytosis was 54.6%. As shown, preoperative leukocytosis exhibited similar abilities to predict recurrence as a preoperative neutrophilia, larger tumor size (≥ 40 mm), parametrial invasion, and lymph node metastasis.

Discussion

The prognostic significance of leukocyte alterations in cervical cancer patients has received attention in recent years. A retrospective analysis showed that the changes in peripheral lymphocyte count after surgery is an independent predictor for recurrence [31]. Moreover, the elevated neutrophil-lymphocyte ratio (NLR) was found to be an independent predictor of deep stromal invasion, lymph node metastasis, and shorter survival in early-stage cervical cancer patients treated with radical hysterectomy [32]. However, the other group reported a conflicting result: the

elevated NLR was not shown to be an independent predictor of shorter survival in surgically-treated early-stage cervical cancer patients [33].

The current study showed that preoperative leukocytosis is an independent predictor of shorter PFS among early-stage cervical cancer patients that are treated with radical hysterectomy. In the present study population, preoperative leukocytosis was detected in 5.6% of patients. Preoperative leukocytosis was found to be associated with larger tumors, deeper stromal invasion, and shorter PFS. These results indicate that cases of early-stage cervical cancer that exhibit leukocytosis involve aggressive disease. When each pathological risk group was examined separately, preoperative leukocytosis was found to be an independent predictor of shorter PFS in patients that displayed intermediate-risk or high-risk pathological factors.

The findings obtained in the current study could have important clinical implications. As 91% of preoperative leukocytosis (21 out of 22) were observed in patients with intermediate-risk or high-risk factors, by performing simple and low-cost peripheral blood examination before performing radical hysterectomy, it may be possible to predict patients who have high probability to require adjuvant chemoradiotherapy after radical hysterectomy. Moreover, it might also be possible to identify patients who are at high risk of developing recurrence after radical hysterectomy, especially among patients who display intermediate-risk or high-risk pathological factors. As preoperative leukocytosis was rarely observed and was not associated with poor prognosis in the low-risk group, the present authors consider that it is not necessary to pay attention to leukocyte count in low-risk patients. However, we have to recognize that the utility of pretreatment leukocytosis or neutrophilia for the selection of primary or adjuvant treatments remains undetermined.

Currently, the underlying mechanisms responsible for the development of preoperative leukocytosis in cervical cancer and the subsequent increase in the aggressiveness of cervical cancer remain to be elucidated. Leukocytosis or neutrophilia can be caused by the upregulated expression of hematological growth factors, including G-CSF, granulocyte macrophage colony-stimulating factor, interleukin (IL)-3, and IL-6 [34]. In the setting of uterine cervical cancer, G-CSF seems to be the most influential of these growth factors [19]. According to recent studies, G-CSF has demonstrated to stimulate tumor progression by facilitating tumor angiogenesis or inducing immune suppression through the increased mobilization of myeloid-derived suppressor cells (MDSC) from the bone marrow [19]. However, it is possible that other tumor-derived factors might also play roles in the development of leukocytosis or neutrophilia and the expansion of MDSC in a G-CSF-independent manner [35]. Moreover, recent investigation suggested that tumor-associated neutrophils (TANs), a subgroup of neutrophils, can function as immunosuppressive cells in the tumor microenvironment [36]. Although the association between pretreatment leukocytosis and the number of tumor-infiltrating TANs in cervical cancer remains unknown, there is a possibility that TANs are associated with the aggressiveness of the cervical cancer displaying pretreatment leukocytosis. Thus, to develop novel treatments for and improve the survival of cervical cancer patients that exhibit preoperative leukocytosis the causative mechanisms should be investigated further.

The limitations of the present study need to be addressed. The first is that this study was conducted at a single institution. The present authors intend to verify these clinical findings in collaborative multi-institutional investigations in the future. The retrospective nature of the current study is another limitation. As this report covers a long period, the contents of patient work-ups;, surgical procedures, and the procedures used to select adjuvant treatment, salvage treatment for recurrent disease, or supportive care have changed, which might have affected the survival of patients. To eliminate these potential biases, prospective investigations need to be conducted. Finally, although the majority of existing reports including the current study have suggested that pretreatment leukocytosis is associated with shorter survival or poorer sensitivity to chemotherapy/radiotherapy, there is a report showing that a cervical cancer patient with marked leukocytosis showed significant response to chemotherapy and eventually achieved complete remission [37]. Thus, the present authors believe that the prognostic significance of pretreatment leukocytosis needs to be further evaluated in large-scale, multi-institutional studies.

Conclusion

In conclusion, the present authors have shown that the presence of preoperative leukocytosis is significantly associated with pathological risk factors exhibited by the cervical cancer resected by radical hysterectomy. Moreover, the presence of preoperative leukocytosis is a predicator of shorter PFS in surgically-treated early-stage cervical cancer patients, especially those with intermediate-risk or high-risk factors. Given the high probability of treatment failure after surgery, novel treatment strategies are urgently needed for such patients.

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