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Prognostic significance of systemic neutrophil and leukocyte alterations in surgically treated endometrial cancer patients: A monoinstitutional study

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HIGHLIGHTS

- Pretreatment neutrophilia was observed in 8.3% of edoetrial cancer patients.
- Pretreatment neutrophilia was associated with conventional risk factors.
- Pretreatment neutrophilia is an independent predictor shorter survival.

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ABSTRACT

Objective. The aim of this study was to investigate the prognostic significance of an elevated neutrophil count at the time of the initial diagnosis in patients with surgically treated endometrial cancer.

Methods. The baseline characteristics and outcome data of patients who were diagnosed with endometrial cancer between January 2000 and December 2010 were collected and retrospectively reviewed. The patients were separated into two groups according to their neutrophil counts. The clinicopathological characteristics and overall survival rates of the two groups were compared. A Cox proportional hazard regression model was used to investigate the prognostic significance of an elevated neutrophil count among patients with surgically treated endometrial cancer.

Results. An elevated neutrophil count was found to be associated with an advanced clinical stage ($P < 0.0001$), lymphovascular space involvement ($P = 0.0003$), cervical involvement ($P = 0.0049$), the proportion of patients that received adjuvant therapy ($P = 0.0020$), elevated NLR ($P < 0.0001$), and treatment failure ($P < 0.0001$). Multivariate analyses demonstrated that age (hazard ratio (HR) = 2.23, 95% confidence interval (95% CI) = 1.30 to 3.91; $P = 0.0035$), clinical stage (HR = 4.72, 95% CI = 2.61 to 8.90; $P < 0.0001$), lymphovascular space involvement (HR = 3.15, 95% CI = 1.60 to 6.68; $P = 0.0007$), an elevated neutrophil count (HR = 2.76, 95% CI = 1.43 to 5.03; $P = 0.0033$), and an elevated white blood cell count (HR = 2.79, 95% CI = 1.50 to 4.96; $P = 0.0017$) were significant predictors of survival.

Conclusion. The elevated neutrophil or leukocyte counts at the time of the initial diagnosis are independent prognostic factors in patients with surgically treated endometrial cancer.

Introduction

Endometrial cancer is the second most common gynecological malignancy (after cervical cancer) in Japan and the fifth most common form of cancer in women worldwide [1].

Surgery followed by tailored adjuvant treatment based on the patient's clinicopathological risk profile is the standard initial treatment for endometrial cancer. Although this approach is potentially curative, a significant number of patients still develop recurrent disease: the risk of recurrence is 10–20% for FIGO stages I–II and 50–70% in stages III–IV disease [2].

Numerous studies have attempted to identify prognostic factors for patients with endometrial cancer. As a result, the histological subtype and grade of the tumor, lymphovascular space involvement (LVSI),

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myometrial invasion, tumors that extend to the cervical stroma, the presence and extent of lymph node metastasis, extra-uterine disease, and the completeness of surgical resection were reported to be significant prognostic factors. However, it is clear that the ability of these conventional risk factors to predict recurrence and estimate survival is insufficient [3–6].

Tumor-related leukocytosis (TRL) is a paraneoplastic syndrome that is occasionally encountered in patients with malignant tumors (especially in those with advanced-stage disease) either at diagnosis or during the course of the disease [7]. We have recently reported that a hematopoietic growth factor that stimulates granulopoiesis, which in turn leads to neutrophilia, is responsible for TRL in uterine cervical cancer patients [8]. In endometrial cancer, recent studies have suggested that TRL occurs in approximately 11–15% of patients and is associated with a poor prognosis [9–11]. However, the leukocyte profiles of TRL-positive endometrial cancer patients and the prognostic significance of such profiles have never been investigated. In the current study, we examined the incidence and prognostic significance of neutrophilia in patients with surgically treated endometrial cancer.

Materials and methods

Patients

Permission to proceed with the data acquisition and analysis was obtained from Osaka University Hospital's institutional review board. A list of patients who were diagnosed with endometrial cancer at Osaka University Hospital from January 2000 to December 2010 was generated from our institutional tumor registry. Then, patients that underwent surgical treatment were identified through a chart review. The surgical procedures consisted of at least total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO). Patients who exhibited grade 2 or 3 endometrioid adenocarcinoma, lesions that had invaded >50% of the myometrium, stromal invasion of the cervix, non-endometrioid histology, or extrauterine disease were treated with TAH, BSO and systematic lymphadenectomy. Among the 508 patients included in the current study, 64 patients with grade 1 endometrioid adenocarcinoma that had invaded <50% of the myometrium and 58 patients who possessed at least one of the abovementioned risk factors underwent TAH plus BSO without lymphadenectomy and were clinically staged according to the findings of preoperative computed tomography. The remaining 386 patients underwent comprehensive surgical staging.

The postoperative adjuvant treatments were tailored to the patients' pathological findings in accordance with the institutional treatment guidelines and those outlined by the Japan Society of Gynecologic Oncology (JSGO) [12]. Adjuvant chemotherapy or radiotherapy was recommended for all patients who displayed any of the following risk factors: a lesion that had invaded >50% of the myometrium, cervical stromal invasion, extrauterine disease, or an unfavorable histological type (grade 3 endometrioid, clear cell, serous papillary, or undifferentiated carcinoma). We have been using adjuvant chemotherapy consisting of paclitaxel, epirubicin, and carboplatin to treat endometrial cancer since 1999 [13]. Patients who refused adjuvant chemotherapy were treated with adjuvant radiotherapy consisting of external beam pelvic radiotherapy without concurrent chemotherapy.

Definitions of neutrophilia, leukocytosis, and neutrophil–lymphocyte ratio

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 and neutrophil counts obtained during these tests were employed in the current analyses. Pretreatment leukocytosis and neutrophilia were defined as the detection of persistent leukocyte or neutrophil counts exceeding 9000/μl and 7200/μl, respectively, on at least two separate occasions. Patients who suffered severe hemorrhaging, were administered corticosteroids, or were suffering from acute or chronic infections were excluded. No HIV-infected patients were included in the current study. Neutrophil–lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

Statistical analysis

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 a two-tailed Fisher's exact test, as appropriate. Spearman's correlation coefficients and 95% confidence intervals (95% CI) were calculated to assess the relationship among the patients' white blood cell (WBC) and neutrophil counts. We performed univariate analysis by comparing the Kaplan–Meier curves for each subgroup with the log-rank test. Overall survival (OS) was defined as the time from the date of the initial surgical procedure to the date of death or the last follow-up. Cox proportional hazard regression analysis was performed to identify independent predictors of survival. P-values of <0.05 were considered to be statistically significant. All analyses were performed using the software JMP®, version 11.0 (SAS Institute, Cary, NC).

Results

Patients

The clinicopathological characteristics of the 508 patients included in this study are summarized in Table 1. The mean age of the patients was 58.0 years. Elevated neutrophil counts ($\geq$7200/μl) were observed in 42 patients (8.3%) at the time of the initial diagnosis, and neutrophilia was present in 5.3%, 11.1%, 10.6%, and 41.2% of the patients with stage I, stage II, stage III, and IV disease, respectively. When the patients with neutrophilia were compared with those without neutrophilia, neutrophilia was found to be associated with an advanced clinical stage, LVSI, and cervical involvement. Moreover, a greater proportion of the patients with neutrophilia received adjuvant therapy.

Neutrophilia as an independent predictor of survival

During follow-up, treatment failures were observed in 61 women (12.2%). A total of 50 women (9.8%) died of endometrial cancer and 5 women died of other diseases. As treatment failure was observed more frequently in the neutrophilia group than in the non-neutrophilia group (Table 1, $p < 0.0001$), we next investigated the prognostic significance of neutrophilia in endometrial cancer patients. As shown in Table 3 and Fig. 1A and B, the univariate analyses demonstrated that in addition to known prognostic factors a neutrophil count of greater than 7200/μl was associated with shorter overall survival. In the multivariate analysis (Table 3), it was found that in addition to age, clinical stage, and LVSI an elevated neutrophil count was also an independent predictor of overall survival (hazard ratio: 2.76; 95% CI: 1.43 to 5.03; $P = 0.0033$). Neutrophilia was found to be an independent prognostic factor in the separate analysis in which cancer-specific survival was used as an endpoint (Supplementary Table 1 and Supplementary Fig. 2A).

Leukocytosis as an independent predictor of survival

As shown, many of the patients with elevated neutrophil counts ($\geq$7200/μl) also had elevated WBC counts (Supplementary Fig. 1A). Among the 42 patients with neutrophilia, 39 had significantly elevated WBC counts ($\geq$9000/μl). Moreover, as a positive correlation was detected between the patients' WBC and neutrophil counts (Supplementary Fig. 1B), we next investigated the prognostic significance of elevated WBC counts among patients with surgically treated endometrial cancer. As shown in Table 2, an elevated WBC count was found to be associated