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Significance of monocyte counts on tumor characteristics and survival outcome of women with endometrial cancer☆

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HIGHLIGHTS

- Monocyte counts obtained prior to hysterectomy-based surgical staging were correlated to tumor characteristics and survival of patients with endometrial cancer.
- Elevated monocyte counts were associated with aggressive tumor behavior including deep myometrial tumor invasion, lymph node metastasis, and advanced stage.
- Elevated monocyte counts were an independent prognostic factor for decreased survival outcome of endometrial cancer patients.

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ABSTRACT

Objective. Tumor-associated macrophages are known to be associated with decreased survival of patients with endometrial cancer. Given the physiological link of circulating monocytes as a progenitor of tumor-associated macrophages, monocyte counts were examined for tumor characteristics and survival in endometrial cancer.

Methods. A retrospective study was conducted to examine consecutive patients with endometrial cancer with all histologic types who underwent hysterectomy-based surgical staging between 2003 and 2013 ($n = 541$). Pre-operative monocyte counts were correlated to patient demographics, pathological findings, complete blood count results, and survival outcomes.

Results. Median monocyte counts were 0.5×10^9/L. Monocyte counts significantly correlated with all other complete blood count components, with neutrophil counts having the most significant association ($r = 0.52$, $p < 0.001$). Elevated monocyte counts (defined as $>0.7 \times 10^9$/L) when compared to lower counts were significantly associated with an increased risk of >50% myometrial tumor invasion (29.2% versus 22.0%, odds ratio [OR] 1.59, 95% confidence interval [CI] 1.01–2.45, $p = 0.045$), pelvic lymph node metastasis (39.0% versus 18.8%, OR 2.76, 95%CI 1.35–5.62, $p = 0.007$), and advanced-stage (stage I through IV, 18.5%, 24.6%, 32.5%, and 41.5%, $p = 0.001$). In survival analysis, elevated monocyte counts were associated with decreased disease-free survival (5-year rates, 71.0% versus 84.5%, $p = 0.001$) and overall survival (77.2% versus 89.3%, $p < 0.001$). In multivariate analysis, elevated monocyte counts remained an independent prognostic factor for decreased disease-free (hazard ratio [HR] 1.74, 95% CI 1.02–2.96, $p = 0.041$) and overall (HR 2.63, 95% CI 1.37–5.05, $p = 0.004$) survival.

Conclusions. Elevated monocyte counts were associated with aggressive tumor features and poor survival outcomes of patients with endometrial cancer.

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1. Introduction

In 2015, endometrial cancer continues to be the most common gynecologic malignancy in the United States, with more than 54,000 new cases estimated to be diagnosed this year [1]. The majority of endometrial cancers are low-grade tumors with early-stage disease, and the mainstay of treatment approach for endometrial cancer is surgery, which includes hysterectomy, adnexectomy, and possible lymphadenectomy. In a fraction of endometrial cancer patients, additional systemic chemotherapy and/or radiotherapy are indicated [2]. Due to the favorable tumor characteristics in endometrial cancer, long remission and cure of disease is possible in the majority of patients. However, despite a multidisciplinary approach with surgery, chemotherapy, and radiotherapy, certain endometrial cancer patients develop disease recurrence where cure can be difficult and challenging. Therefore, novel approaches for identifying these tumors that are likely to recur may allow for optimization of treatment in these patients and improved survival.

The interaction between host immune cells and cancer cells has been identified as a key to tumor suppression or progression in various types of malignancies including endometrial cancer [3,4]. Tumor-associated macrophages (TAMs) appear to be a key mediator of this interaction, and multiple studies have shown that increased accumulation of TAMs in the tumor site of the uterus is associated with aggressive tumor behaviors (higher stage and grade, lymphovascular space invasion [LVSI], and deep myometrial tumor invasion) and decreased survival outcome of endometrial cancer patients [5–10]. TAMs are the differentiated form of monocytes outside of the vasculature (monocyte–macrophage lineage) [11,12], and are one of the inflammatory cell types found in the tumor microenvironment known to have a pivotal role in the immune response to cancer [13,14]. That is, TAMs in the tumor microenvironment are recruited from tumors and differentiated into polarized M2 macrophages that are a source and target of cytokines, chemokines, and growth factors, which results in cancer progression and suppression of anti-tumor immune system [12,15]. While TAMs adversely impact the prognosis of endometrial cancer patients, the association of monocyte counts and endometrial cancer progression has not been well studied. Given that circulating monocytes in blood vessels function as a precursor and potential origin of TAMs, monocyte counts were examined and correlated to tumor characteristics and survival outcomes of endometrial cancer patients in this study.

2. Patients and Methods

2.1. Eligibility

After Institutional Review Board (IRB) approval was obtained at the University of Southern California, the institutional database for endometrial cancer was utilized to identify the patients. This study included consecutive endometrial cancer patients with all histologic subtypes who were treated with hysterectomy-based surgical staging at Los Angeles County Medical Center between April 2003 and March 2013. Excluded cases were those without laboratory results at the time of cancer diagnosis, or if the final diagnosis was uterine sarcoma or endometrial hyperplasia. Among eligible cases, the following information were abstracted from medical records: (*i*) patient demographics, (*ii*) pathology results for hysterectomy-based surgical staging, (*iii*) laboratory results for complete blood counts obtained at the time of endometrial cancer diagnosis prior to surgical staging, and (*iv*) survival outcome. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines were consulted for reporting in a retrospective cohort study [16]. Some of the patients in this study were within the context of our previous studies [17–20].

2.2. Clinical information

Archived medical records were reviewed to abstract the clinical information for eligible cases. (*i*) Patient demographics included age at surgery, ethnicity, and body mass index (BMI, expressed in kg/m^2). (*ii*) Pathology results for hysterectomy-based surgical staging included histology subtype, grade, stage, depth of myometrial tumor invasion (%), presence of LVSI, and pelvic/aortic lymph node metastasis. For lymph node results, total number of sampled nodes and number of positive lymph nodes were also recorded. (*iii*) Laboratory results for complete blood counts included absolute neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts (expressed in $\times 10^9$/L), hemoglobin (expressed in g/dL), and platelet counts (expressed in $\times 10^9$/L) were abstracted. (*iv*) For survival outcomes, disease-free survival (DFS) and disease-specific overall survival (OS) were abstracted.

2.3. Definition

The cutoff values for complete blood counts were based on the previous studies for endometrial cancer: Neutrophil-to-lymphocyte ratio (N/L ratio, defined as the proportional ratio of absolute neutrophil counts over lymphocyte counts) of 3.0 [21], hemoglobin of 12.0 g/dL [22], and platelet of 400×10^9/L [20]. Because no prior study examined the significance of monocyte counts on endometrial cancer survival, monocyte counts were categorized into three groups (1%–33%ile ≤0.4, 34%–66%ile 0.5–0.6, and 67%–100%ile, $\geq 0.7 \times 10^9$/L). Various cutoff values for monocyte counts were examined and a count of 0.7×10^9/L was confirmed as the cutoff value to maximize the survival outcomes for DFS and OS (Table S1A). Neutrophil counts of 5.5×10^9/L were used for the cutoff value to maximize the survival outcome for DFS and OS in our study (Table S1B). Lymphocyte, eosinophil, and basophil counts were not associated with survival outcome and therefore median values were used for the cutoff.

Lymph node ratio (LNR) was defined as the percent ratio of positive metastatic lymph node number per total sampled lymph nodes per case [23]. Endometrial cancer grade was based on the International Federation of Gynecology and Obstetrics (FIGO), and cancer stage was reclassified based on the 2009 FIGO staging system [24]. DFS was defined as the time interval between hysterectomy-based surgical staging and the date of first recurrence or the date of last follow-up date if there was no recurrence. OS was defined as the time interval between the date of hysterectomy-based surgical staging and the date of death due to endometrial cancer of the last follow-up date if the patient was alive.

2.4. Statistical analysis

The primary objective of the analysis was to correlate monocyte counts to tumor factors from the hysterectomy specimen. The secondary objective of the analysis was to determine the survival significance of monocyte counts in endometrial cancer patients. Continuous variables were examined for normality by Kolmogorov–Smirnov test expressed with mean (±standard deviation) or median (range) as appropriate, and Spearman's correlation coefficient was performed for statistical evaluation among the continuous variables. Median values of monocyte counts among multiple groups were examined by Mann–Whitney *U* test or Kruskal–Wallis test as appropriate. Using a cutoff value of elevated monocyte counts ($\geq 0.7 \times 10^9$/L), the statistical accuracy for pelvic and aortic lymph node metastasis was determined (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], and accuracy). Categorical or ordinal variables were expressed as a percentage (%), and Fisher's exact test or chi-square test was used to determine the statistical significance expressed with odds ratio (OR) and 95% confidence interval (CI).

For survival analysis, log-rank test was used for univariate analysis. A Cox proportional hazard regression model was used for multivariate analysis with conditional backward method given the degree of