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学位論文

Correlation of bone marrow 2-deoxy-2-[^{18}F]fluoro-D-glucose uptake with systemic inflammation in patients with newly diagnosed endometrial cancer

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Correlation of bone marrow 2-deoxy-2-[^{18}F]fluoro-D-glucose uptake with systemic inflammation in patients with newly diagnosed endometrial cancer

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Objective **To clarify the relationship between 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) uptake of bone marrow and systemic inflammation in patients with newly diagnosed endometrial cancer.**

Methods **A total of 119 patients with untreated endometrial cancer underwent FDG PET/computed tomography (CT). For bone marrow FDG uptake, the mean standardized uptake value (SUVmean) of the five vertebrae (T11-12 and L3-L5) was measured and averaged (bone marrow SUV). The bone marrow-to-liver ratio (BLR) was calculated by dividing the bone marrow SUV by the SUVmean of the normal liver. FDG PET parameters were correlated with white blood cell count, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and C-reactive protein (CRP), albumin, and hemoglobin levels. They were also correlated with FIGO stage.**

Results **Bone marrow SUV and BLR showed significant positive correlations with white blood cell count, NLR, and CRP level and significant negative correlations with albumin level. BLR also showed a significant positive correlation with PLR. No significant differences in bone marrow SUV and BLR were apparent according to FIGO stage.**

Conclusion **Pretreatment FDG PET/CT in patients with newly diagnosed endometrial cancer may provide information on host systemic inflammation as assessed by bone marrow FDG uptake.** ***Nucl Med Commun*** **XXX: 000–000** **Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Endometrial cancer is the most common gynecological malignancy in Western countries [1]. Outcomes in patients with malignant tumors are now known to be determined by not only tumor characteristics but also patient-related factors such as nutritional, functional, and immunological declines [2]. It has been reported that inflammatory microenvironment plays critical roles in carcinogenesis, invasion, and metastasis [3,4]. Furthermore, inflammatory microenvironment has become an attractive target for cancer therapy [5]. It has also become widely recognized that neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), C-reactive protein (CRP), and other systemic inflammatory markers are important prognostic factors in such patients [2,3,6,7].

PET with 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) is a useful molecular imaging modality for staging, restaging, and assessment of the therapeutic response for endometrial cancer [8]. The preoperative FDG PET/computed tomography (CT) in patients with endometrial cancer is considered as an important indicator of tumor aggressiveness that may predict a poor prognosis [9]. Furthermore, a recent study found that bone marrow FDG uptake reflects bone marrow activation in response to systemic inflammation [10]. Several studies have focused on the relationship between bone marrow FDG uptake and systemic inflammatory response and evaluating its impact on prognosis, in patients with various malignant tumors [11–18]. However, no studies seem to have been published on FDG PET and systemic inflammatory markers in patients with endometrial cancer.

This prompted us to investigate the relationship between bone marrow FDG uptake and host systemic inflammation in patients with newly diagnosed endometrial cancer.

Materials and methods

Patients

This retrospective research protocol was approved by our institutional ethics review committee with the requirement for obtaining informed consent waived. The medical records of patients who underwent FDG PET/CT from May 2010 to February 2021 were reviewed. The

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inclusion criteria were as follows: patients with newly diagnosed endometrial cancer or carcinosarcoma, patients who were scheduled for surgery, and patients who underwent FDG PET/CT scan before therapy. The exclusion criteria were as follows: patients who had anticancer therapy before FDG PET/CT scan, patients who had concurrent liver, hematologic, or infectious disease, and patients who had a history of chronic inflammatory, autoimmune disease, another malignancy, or bone marrow disease. Finally, 119 female patients (mean age, 60 years; age range, 30–93 years) were enrolled in the study. The 2009 Staging Criteria of the International Federation of Gynecology and Obstetrics (FIGO) were used [19]. There were 81 patients in stage I, 14 in stage II, 19 in stage III, and 5 in stage IV. The distribution of tumor histology was as follows: 25 endometrioid adenocarcinoma G1, 34 endometrioid adenocarcinoma G2, 9 endometrioid adenocarcinoma G3, 12 serous adenocarcinoma, 4 mucinous adenocarcinoma, 1 clear cell adenocarcinoma, 24 mixed carcinoma, and 11 carcinosarcoma.

Laboratory data included white blood cell, neutrophil, lymphocyte, and platelet counts and hemoglobin, CRP, and albumin levels, which were measured within 29 days of the date of the PET/CT scan (median 7 days). During this period, no patients were found to have any events that might affect laboratory data such as fever or infectious symptoms. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. The PLR was also calculated by dividing the platelet count by the lymphocyte count.

Fluoro-D-glucose PET/computed tomography imaging and analysis

FDG was manufactured using an automated synthesis system with HM-18 cyclotron (QUPID; Sumitomo Heavy Industries Ltd, Tokyo, Japan).

All acquisitions were performed using a Biograph mCT 64-slice PET/CT scanner (Siemens Healthcare, Erlangen, Germany) with an axial field of view of 21.6 cm. Patients fasted for at least 5 h prior to FDG administration, and a normal glucose level in the peripheral blood was confirmed prior to injection. Emission data were obtained 90 min after intravenous injection of FDG (5 MBq/kg) from the midcranium to proximal thighs (2 min per bed position). Unenhanced low-dose CT of the same area was performed for attenuation correction and image fusion. PET data were reconstructed using a Gaussian filter with an ordered subset expectation maximization algorithm, incorporating correction with point-spread function and time-of-flight model (2 iterations and 21 subsets).

To measure FDG uptake of the bone marrow, a volume of interest (VOI) was drawn over the vertebral body of each of five vertebrae (T11-12 and L3-L5, unless a pathologic condition such as compression fracture was present) by a board-certified nuclear medicine physician. The mean standardized uptake value (SUV) (SUVmean) of each VOI was measured using an automatic isocontour set at 75 % of the maximum SUV. Average SUVmean of the five selected vertebrae was calculated and defined as bone marrow SUV. The SUVmean of the normal liver was also measured by drawing a 2 cm-sized VOI in the right lobe of the liver. The bone marrow-to-liver ratio (BLR) was calculated by dividing the bone marrow SUV by the SUVmean of the liver.

Statistical analyses

The data were analyzed using the SPSS statistical software (version 26; IBM). The nonparametric Spearman's rank correlation coefficients were used to determine the degree of correlation between the FDG PET parameters and laboratory data. Differences in FDG PET parameters among FIGO stage were compared using the Kruskal–Wallis test. The Bonferroni-corrected Mann–Whitney test was used for the post hoc analysis. Differences were considered statistically significant at a P value of less than 0.05.

Results

Sixty-three of all patients (52.9 %) showed higher FDG uptake of bone marrow than that of the liver (BLR > 1.0). The mean (±SD) bone marrow SUV and BLR were 2.29 ± 0.51 and 1.06 ± 0.26, respectively. Typical FDG PET images from BLR ≤ 1.0 group and BLR > 1.0 group are shown in Figs. 1 and 2, respectively.

Table 1 shows the relationship between FDG uptake of bone marrow and hematologic parameters and serum inflammatory markers. Bone marrow SUV showed significant positive correlations with white blood cell count, NLR, and CRP level and a significant negative correlation with the albumin level. BLR showed significant positive correlations with white blood cell count (Fig. 3a), NLR (Fig. 3b), PLR (Fig. 3c), and CRP level (Fig. 3d) and a significant negative correlation with albumin level (Fig. 3e). In contrast, bone marrow SUV and BLR did not show significant correlations with the hemoglobin level.

According to the FIGO stage classification, the mean (±SD) bone marrow SUV was 2.27 ± 0.50 in stage I, 2.30 ± 0.48 in stage II, 2.42 ± 0.45 in stage III, and 2.23 ± 0.94 in stage IV. The corresponding values of BLR were 1.04 ± 0.24, 1.07 ± 0.24, 1.12 ± 0.29, and 1.11 ± 0.39, respectively. No significant differences in bone marrow SUV or BLR were shown according to the FIGO stage (P = 0.444 and 0.649, respectively).

Discussion

This study focused on the relationship between FDG uptake of bone marrow and host systemic inflammation in patients with newly diagnosed endometrial cancer. Inflammation is now understood to be one of the hallmarks of cancer [3]. As the inflammatory response

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Fig. 1

Pretreatment FDG PET maximum intensity projection image of a 59-year-old female with stage I endometrial mixed carcinoma shows slight bone marrow uptake (bone marrow SUV = 1.52; BLR = 0.78). NLR, PLR, CRP level, and albumin level were 1.09, 115.52, 0.1 mg/l, and 47 g/l, respectively.

Fig. 2

Pretreatment FDG PET maximum intensity projection image of a 60-year-old female with stage I endometrioid adenocarcinoma G3 shows markedly increased bone marrow uptake (bone marrow SUV = 3.10, BLR = 1.77). NLR, PLR, CRP level, and albumin level were 4.46, 424.37, 20.8 mg/l, and 36 g/l, respectively.

is related with tumor progression, serum inflammatory markers have been shown to have significant prognostic value, and they are considered to be a useful tool for predicting the clinical outcome, in various malignant tumors [6,20,21]. In addition, several studies have focused to find imaging parameter for estimating systemic inflammatory response using FDG PET/CT [11–18]. Therefore, the present results suggesting that bone marrow FDG uptake is associated with host systemic inflammation are of major interest.

Inoue *et al.* [22] suggested that bone marrow FDG uptake greater than or equal to that of the liver may indicate bone marrow activation. A previous investigation reported that mean bone marrow SUV and BLR in 40 normal subjects were 1.31 ± 0.21 and 0.60 ± 0.10, respectively [11]. The corresponding values (2.29 ± 0.51 and 1.06 ± 0.26, respectively) in the present data in endometrial cancer patients were higher. Bone marrow FDG uptake in patients with malignant tumors compared with normal subjects may reflect bone marrow activation in response to systemic inflammation. Bural *et al.* [23] demonstrated higher bone marrow FDG uptake in patients with active lung cancer than in those without active disease, reflecting a systemic immune response to malignant tumors.

Recent studies have documented that bone marrow FDG uptake correlates with systemic inflammatory markers

Table 1 Relationship between FDG uptake of bone marrow, hematologic parameters, and serum inflammatory markers in patients with newly diagnosed endometrial cancer

	Bone marrow SUV		BLR	
Laboratory data	*ρ*	*P* value	*ρ*	*P* value
White blood cell	0.390	<0.001	0.364	<0.001
NLR	0.211	0.021	0.278	0.002
PLR	0.058	0.532	0.197	0.032
CRP	0.337	<0.001	0.319	<0.001
Hemoglobin	−0.074	0.426	−0.157	0.088
Albumin	−0.199	0.030	−0.196	0.032

BLR, bone marrow-to-liver ratio; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SUV, standardized uptake value.

including CRP and NLR in various types of cancer [10–16]. As for gynecological malignancies, one retrospective study by Lee *et al.* [11] focused on this topic. They evaluated bone marrow FDG uptake in 145 patients with uterine cervical cancer and found BLR to be significantly related to the white blood cell count, NLR, and PLR, consistent with the results of the present study [11]. Neutrophils and platelets promote tumor growth and metastasis, and lymphocytes play important roles in antitumor cellular immunity [4]. NLR and PLR are, thus, recognized to be useful indicators of the systemic inflammatory response to malignant tumors. Murata *et al.* [10] considered bone marrow FDG uptake to reflect mainly

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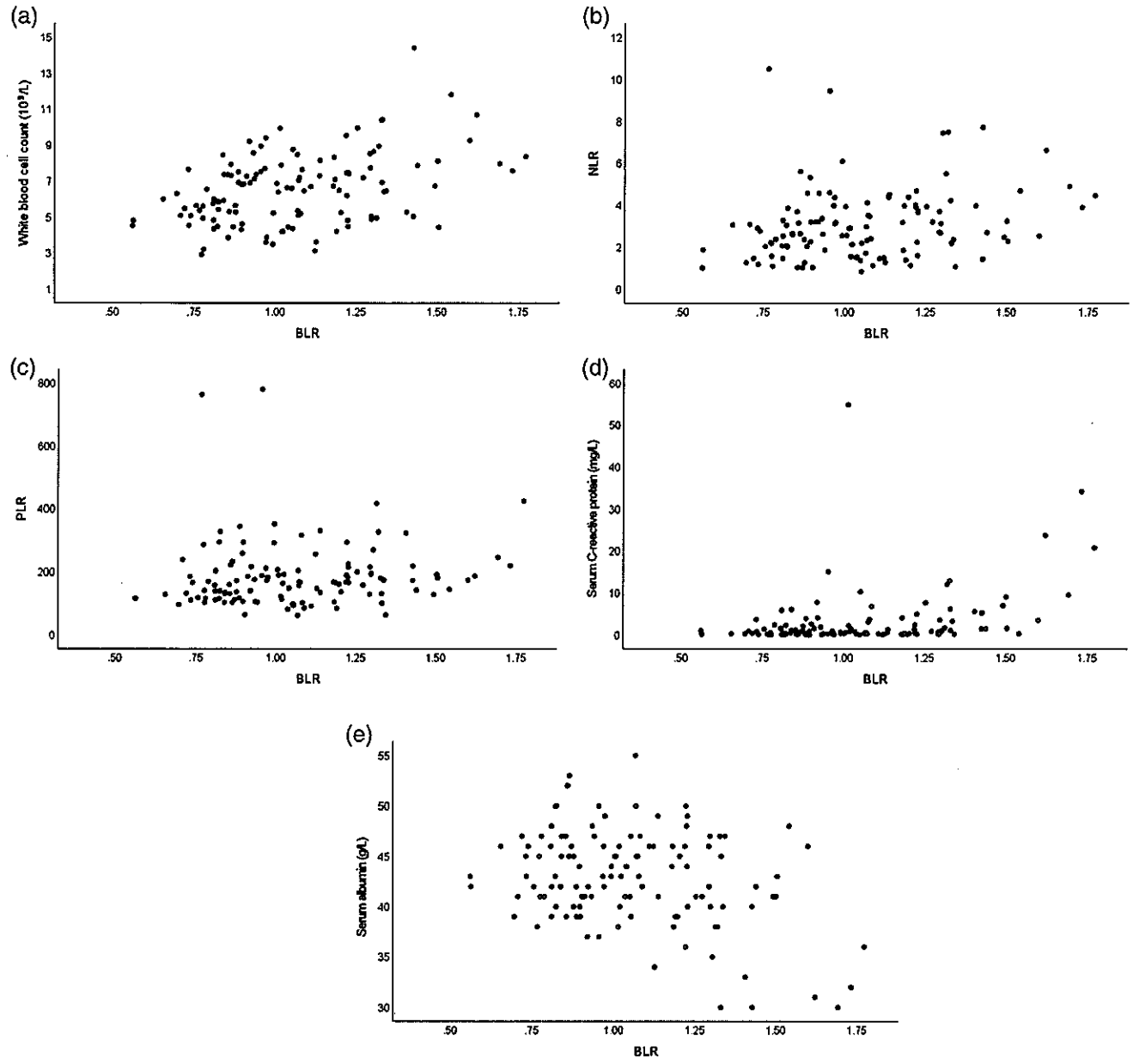
Fig. 3



Scatter plot showing the correlation between BLR and white blood cell count (a) ($\rho = 0.364$; P value < 0.001), NLR (b) ($\rho = 0.278$; P value $= 0.002$), PLR (c) ($\rho = 0.197$; P value $= 0.032$), CRP level (d) ($\rho = -0.319$; P value < 0.001), and albumin level (e) ($\rho = -0.196$; P value $= 0.032$).

the glucose metabolism of granulocyte progenitors, exhibiting the systemic inflammatory response evoked by the immune system. No reports, however, seem to have been published on this topic in patients with endometrial cancer. However, bone marrow FDG uptake in patients with malignancies has been significantly correlated with serum inflammatory markers, suggesting that it reflects the bone marrow activation elicited in response to systemic inflammation and so may serve as a useful imaging biomarker to assess systemic inflammation [10]. Bone marrow SUV has shown a significant positive correlation with CRP level in patients with colorectal cancer [16], consistent with the present results. In patients with cancer, the CRP level may increase due to its inflammation-related production [24]. Although patients in the present study had no other obvious inflammatory lesions detected by FDG PET other than primary and metastatic lesions, we should also be aware of other inflammation that affects the host systemic inflammation. However, CRP is a nonspecific

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marker of inflammation. Several studies have shown that CRP levels can be reduced with smoking cessation and weight loss [25,26]. Hypoalbuminemia is common in patients with advanced cancer, and is usually considered a marker of malnutrition and cachexia. Lee *et al.* [11] reported that BLR demonstrated a significant negative correlation with albumin level in patients with cervical cancer, consistent with the present results. Further additional studies are required to determine the clinical relationship between CRP and albumin levels and bone marrow FDG uptake.

In the present study, no significant differences in bone marrow SUV or BLR were noted according to FIGO stage. Xu *et al.* [21] demonstrated that higher FIGO stage was significantly correlated with higher systemic inflammatory markers in patients with cervical cancer. Inflammation can promote the development, progression and metastasis of cancer [5]. In contrast, a previous study of colorectal cancer by McSorley *et al.* [27] showed that NLR was not associated with T stage or N stage. Bone marrow FDG uptake could be due to various conditions including tumor and nontumor factors. Among the various tumor factors, Lee *et al.* [11] demonstrated that bone marrow FDG uptake was significantly associated with tumor size and FDG PET parameters of primary tumor such as maximum SUV, metabolic tumor volume, and total lesion glycolysis, in patients with head and neck cancer [18]. This may indicate an enhanced inflammatory response in patients with advanced cancer. Other causes such as cancer micrometastases, hematological disorders, or increased cytokines associated with malignancy should also be considered. Inoue *et al.* [22] reported a significant influence of red marrow hyperplasia to bone marrow FDG uptake although no correlation was shown between bone marrow FDG uptake and hemoglobin level in the present study. Bone marrow FDG uptake might be also affected by glucose metabolism of erythroid cells in the bone marrow [11]. Further studies including bone marrow aspiration and serum cytokine levels are needed to identify the mechanism of bone marrow FDG uptake.

The main limitations of this study are its retrospective design and small sample-size from a single institution. Another limitation is the interval between laboratory tests and PET/CT scan (median 7 days). We did not analyze the association between bone marrow FDG uptake and tumor and nontumor factors. We did not follow up patients to justify the relationship between the inflammatory response and tumor behavior. The association of bone marrow FDG uptake with the prognosis was not investigated here although a significant association between bone marrow FDG uptake and survival has been shown in patients with cervical cancer, nonsmall cell lung cancer, and head and neck cancer [11,13,17]. Mantovani *et al.* [28] reported that 'smoldering' inflammation in the tumor microenvironment has many tumor-promoting effects, such as enhancing proliferation and survival of malignant cells, promoting angiogenesis and metastasis, and disrupting adaptive immune responses. Because cancer-related inflammation has become an attractive target for cancer therapy, patients with high bone marrow FDG uptake may be good candidates for future treatment to control it [5]. Additional large prospective studies will be required to fully characterize the relationship between FDG PET/CT and systemic inflammatory response in patients with endometrial cancer.

In conclusion, our preliminary findings show that pretreatment FDG PET/CT in patients with newly diagnosed endometrial cancer may provide information on the host systemic inflammation that may be assessed by bone marrow FDG uptake.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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