Prediction of Recurrence by Preoperative Intratumoral FDG Uptake Heterogeneity in Endometrioid Endometrial Cancer

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Abstract

PURPOSE: To investigate the prognostic value of preoperative intratumoral ^{18}F-FDG uptake heterogeneity (IFH) derived from positron emission tomography (PET)/computed tomography (CT) in patients with endometrioid endometrial cancer. *METHODS:* We retrospectively evaluated clinicopathological data from patients with pathologically proven endometrioid endometrial cancer who had undergone ^{18}F-FDG PET/CT scans before surgery. Patients were divided into two groups according to their IFH. The main outcome measure was disease-free survival (DFS). *RESULTS:* Between January 2010 and January 2015, data from 72 patients were available for analysis. The median duration of DFS was 23 months (range, 6 to 57 months), and 4 (5.6%) patients experienced recurrence. There were significant differences in tumor size, IFH, and DFS between patients with and without recurrence. In regression analysis, high IFH value [P = .007, hazard ratio (HR) 2.545, 95% confidence interval (CI) 1.468-8.674] was the only independent risk factor for recurrence. The Kaplan-Meier survival graphs showed that DFS significantly differed in groups categorized based on IFH (P < .001, log-rank test). CONCLUSIONS: Preoperative IFH measured by ^{18}F-FDG PET/CT was associated with recurrence of endometrioid endometrial cancer. The finding supports evidence that FDG-based heterogeneity can be a novel and useful predictor of endometrioid endometrial cancer recurrence.

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Introduction

The incidence of endometrial cancer is rapidly increasing worldwide, with the highest disease burden reported in developed countries. In the United States, endometrial cancer has been the most common gynecologic malignancy with more than 60,000 newly diagnosed cases projected for 2016 [1], and there will be a doubling in the number of women diagnosed with endometrial cancer by the year 2030 to 122,000 cases per year [2]. Such trend is global, and the age-standardized incidence of endometrial cancer has been doubled in South Korea [3,4]. However, endometrial cancer has been under-studied and remains an underfunded field of research.

^{18}F-FDG positron emission tomography (PET)/computed to-mography (CT) combines morphologic and physiologic techniques and is the preferred imaging method especially in clinical oncology [5], and previous studies have suggested beneficial role of preoperative ^{18}F-FDG PET/CT in endometrial cancer [6–9]. ^{18}F-FDG uptake in

tissue is a useful indicator of tumor metabolism, and the maximum standardized uptake value (SUV$_{max}$) reflects the highest metabolic activity within the tumor. There has been increasing interest in assessing the tumor heterogeneity and, specifically, intratumoral ^{18}F-FDG uptake heterogeneity (IFH) [10]. The association between IFH and prognosis has been reported in several malignancies [10–13]. Several physiological processes including glucose metabolism, necrosis,

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vascularization, and angiogenesis were regarded as having correlation with heterogeneous distribution of ^{18}F-FDG PET activity in the same tumor [14,15]. Although there were several studies on the clinical role of IFH in predicting prognosis in various cancers [16–18], there is no study on the ^{18}F-FDG heterogeneity in endometrial cancer.

The objective of this study was to investigate the prognostic value of preoperative intratumoral IFH in patients with endometrioid endometrial cancer. For this purpose, we investigated the relationship between the IFH and various clinical and PET/CT parameters.

Materials and Methods

Patients

We retrospectively reviewed all consecutive patients with histologically biopsy proven endometrioid endometrial cancer who underwent preoperative ^{18}F-FDG PET/CT imaging between January 2010 and January 2015. The diagnoses were established through preoperative endometrial biopsy, and stage was assessed according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria for surgical staging. All clinicopathological and imaging data from patients were collected and reviewed. Patients were required to have undergone both preoperative integrated ^{18}F-FDG PET/CT imaging in the 2 weeks prior to surgery. Patients were excluded from analysis if 1) they had another malignant disease; 2) they had nonendometrioid endometrial cancer; 3) they had a follow-up duration <6 months; 4) they received a primary treatment other than surgery, such as neoadjuvant chemotherapy or preoperative radiation; 5) they had received scan at outside institution; or 6) their scan had no sign of FDG uptake abnormality. After treatment, all patients were clinically and radiologically followed up. The study protocol was approved by the institutional review board, and informed consent was waived due to its retrospective design.

Demographic and clinical characteristics and survival data were obtained from the patients' medical records and institutional tumor records. Tumor histology, grade, and size were obtained from the surgical pathology report.

PET/CT Technique

Patients were examined using an integrated Biograph PET/CT scanner (Siemens Medical Solutions, USA). Requested minimum fasting time for ^{18}F-FDG PET/CT imaging was 6 hours, and diuretics were not used for preparation. Fasting blood sugar level was checked using a commercially provided portable glucometer (Accu-Chek; Roche, Indianapolis, IN). Approximately 0.14 mCi/kg body weight of FDG was administered intravenously 1 hour prior to imaging. After voiding, CT was performed before PET, and the resulting data were used to generate an attenuation correction map for PET. The following parameters were used for CT: 80 mA, 120 kV, 5-mm section thickness, 0.5 second per rotation, and reconstruction onto a 512 × 512 matrix. Each PET scan was acquired from skull base to proximal thigh in three-dimensional row action maximum likelihood algorithm mode with 4 iterations, 8 subsets, and 4.8-mm full-width half-maximum reconstruction onto a 512 × 512 matrix. A total of 7 to 9 bed positions were examined for PET acquisition, with 2.5 min/bed position.

Image Analysis

^{18}F-FDG PET/CT scans were reviewed by two experienced nuclear physicians, and intensity values were converted to SUVs.

Findings were recorded by consensus, and the nuclear physicians were masked to all other clinical and imaging information. The contour around the target lesions inside the boundaries was automatically produced, and the voxels presenting a threshold of 40% SUV_{max} in the volume of interest within the contouring margin were incorporated to define the precise tumor volumes (Figure 1).

The SUV_{max} and average SUV (SUV_{avg}) were then quantitatively used to determine ^{18}F-FDG avidity. SUV was defined as the concentration of ^{18}F-FDG divided by the injected dose, corrected for the body weight of the patient and radioactive decay at scanning time (SUV = activity concentration/[injected dose/body weight]).

Intratumoral FDG Heterogeneity Analysis

In the current analysis, coefficient of variation (CV) was chosen to calculate tumor heterogeneity. CV is one of the representative parameters of global level that has been reported to predict therapy response and prognosis in several cancers [19]. CV was defined as the standard deviation (SD) of SUVs divided by the SUV_{avg} within the automatically delineated tumor volume, expressed as CV = SD of SUVs/SUV_{avg}.

Clinical Endpoints and Follow-Up

To determine recurrence or death and other clinical characteristics, serial data were collected from medical records. Surveillance after treatment was performed according to the institutional protocol: every 2 months for 12 months, then every 3 months for 18 months followed by every 6 months for 36 months. Gynecological examination and test for serum CA-125 were performed at every visit, and imaging checkup using CT or magnetic resonance imaging was performed every 6 months. ^{18}F-FDG PET/CT was considered when recurrence was suspected during surveillance.

Disease-free survival (DFS) was defined as the time from the date of surgery to date of the first finding on clinical or imaging examination that suggested local, regional, or distant disease recurrence. Recurrent tumor and distant metastasis were diagnosed based on either a positive biopsy or unequivocal clinical or radiographic evidence of progression.

Statistical Analysis

We tried to determine the prognostic value of preoperative ^{18}F-FDG PET/CT parameters for DFS. Kaplan-Meier estimates and the log-rank test were done to assess the equality of the survival functions across variables in the DFS analysis. The Cox proportional hazard model was used to evaluate prognostic variables, and hazard ratio (HR) with 95% confidence interval (95% CI) was presented. A P value < .05 was considered statistically significant. All analyses were performed using SPSS software for Windows (version 19.0; IBM SPSS, Somers, NY).

Results

Patient Characteristics

During the study period, 217 patients at our institution were newly diagnosed with endometrioid endometrial cancer, and 125 of these patients underwent PET/CT prior to primary treatment. However, scans from 53 patients were unavailable for SUV measurement: scans from 34 patients were unavailable for analysis with current workstation because their scans were performed at outside institutions, and 19 scans had no sign of FDG uptake abnormality. Eventually, scans from 72 of these patients (median age, 55 years;
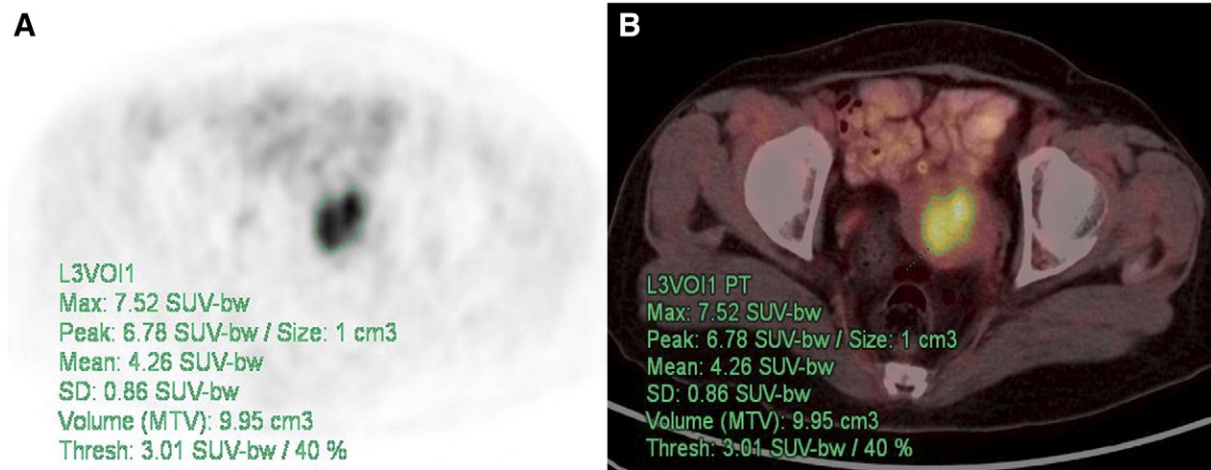
Figure 1. Measurement of IFH. PET (A) and PET/CT (B) for IFH measurement using an SUV-based automated contouring program in a 64-year-old female patient. Transaxial PET or PET/CT images show hypermetabolic lesion with heterogeneous distribution of FDG inside uterine cavity.

range, 28-76 years) were eligible for IFH analysis. The median follow-up for surviving patients was 23 months (range, 6-57 months). Patient clinicopathological findings and preoperative PET/CT findings are summarized in Table 1.

Measurement of Cutoff Value for Intratumoral Heterogeneity

The receiver-operating characteristic (ROC) curves were used to analyze the IFH in relation to DFS. IFH at an SUV threshold of 40% was used for ROC analysis, and area under the curve (AUC) of the ROC curve of IFH was 0.886 (P = .010, 95% CI 0.751-1.000), and 0.2651 was determined as the optimal threshold (Figure 2). The sensitivity at this cutoff value was 0.750, and the specificity was 0.897.
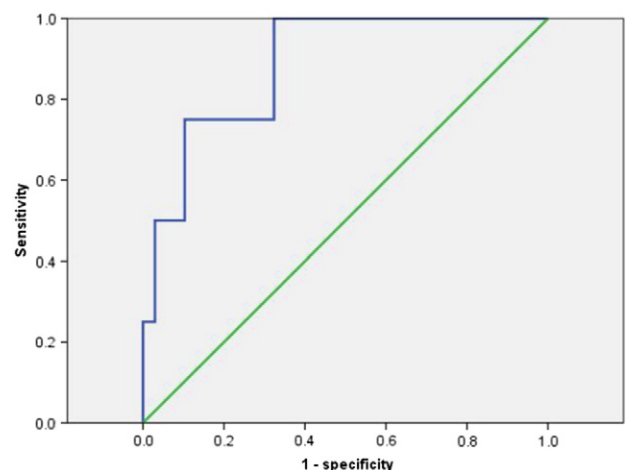
Prediction of Recurrence

Tables 2 and 3 summarize the results of univariate and multivariate regression analyses of prognostic factors for DFS, respectively. Univariate regression analysis revealed that high IFH value (P = .012, HR 9.608, 95% CI 1.182-7.809) was associated with recurrence (Table 2). Large tumor size (P = .053, HR 1.356, 95% CI 0.996-1.845) and advanced FIGO stage (P = .071, HR 8.018,

95% CI 0.834-77.124) showed borderline significance. In multivariate regression analysis, high IFH value (P = .007, HR 2.545, 95% CI 1.468-8.674) was the only independent risk factor for recurrence (Table 3). Kaplan-Meier survival graphs in Figure 3 depict that DFS significantly differed in groups categorized based on threshold IFH (P < .001, log-rank test).

Summary of Patients with Recurrence

Table 4 shows the clinicopathological characteristics of four patients who experienced recurrence after treatment for endometrioid endometrial cancer. Two patients had FIGO stage III disease, one had stage II, and another had IVB, respectively. DFS ranged from 6 to 22 months, and the SUV_{max} ranged from 8.95 to 20.42. Patients with stage IVB had the lowest IFH value, whereas patients with stage II had the highest IFH value (range, 0.2521-0.2873).

Table 1. Clinicopathological Characteristics of Patients Who Underwent PET/CT before Operation for Endometrioid Endometrial Cancer (n = 72)

Characteristic	Patients	%
Age, median (range)	55 (28-76)	
Median DFS, months (range)	23 (6-57)	
FIGO stage		
I	49	68.1
II	3	4.2
III	16	22.2
IV	4	5.6
Tumor grade		
1	33	45.8
2	28	38.9
3	11	15.3
Recurrence	5	6.9
Median tumor size, cm (range)	3.5 (1-12)	
Median SUV_{max} (range)	11.96 (2.73-36.10)	
Median IFH (range)	0.2434 (0.17-0.29)	
Recurrence	4	5.6

Figure 2. ROC curve analysis for determination of the cutoff value of IFH for predicting recurrence in patients with endometrial cancer. Area under the ROC curve of IFH was 0.886 (P = .010, 95% CI 0.751-1.000), and 0.2651 was determined as the optimal threshold.

Table 2. Univariate Regression Analyses of Prognostic Factors for DFS in Patients with Endometrial Cancer

Variables	Test for Progression-Free Survival	HR	95% CI	P
Age (years)		0.978	0.893-1.071	.634
FIGO stage	III, IV vs I, II	8.018	0.834-77.124	.071
Tumor grade	3 vs 1, 2	0.032	0.000-598.471	.494
Tumor size		1.356	0.996-1.845	.053
Deep myometrial invasion	Present vs absent	1.580	0.222-11.224	.648
LVSI	Present vs absent	2.791	0.393-19.836	.305
LN metastasis	Present vs absent	1.627	0.168-15.714	.674
SUV_{max}		1.023	0.919-1.139	.677
IFH		9.608	1.182-7.809	.012

Differences between Recurrent and Nonrecurrent Groups

Table 5 summarizes the clinicopathological and ^{18}F-FDG PET/CT imaging–derived characteristics of patients with and without recurrence. There were significant differences in tumor size (P = .004), IFH (P = .018), and DFS (P = .022) between patients with and without recurrence.

Discussion

The principal finding of the current study was that preoperative IFH measured by ^{18}F-FDG PET/CT was significantly associated with recurrence in endometrioid endometrial cancer. To the best of our knowledge, this is the first report investigating the prognostic value of preoperative IFH in endometrioid endometrial cancer. The result depicts that ^{18}F-FDG–based heterogeneity can be a useful and potential predictor of patient recurrence before treatment in patients with endometrioid endometrial cancer.

Despite improved understanding of the pathogenesis of endometrial cancer, the prognosis for those with recurrent or metastatic disease, the options are few, and the prognosis is poor [20]. In this view, identification of patients with a poor prognosis who may benefit from aggressive surveillance and treatment is very important.
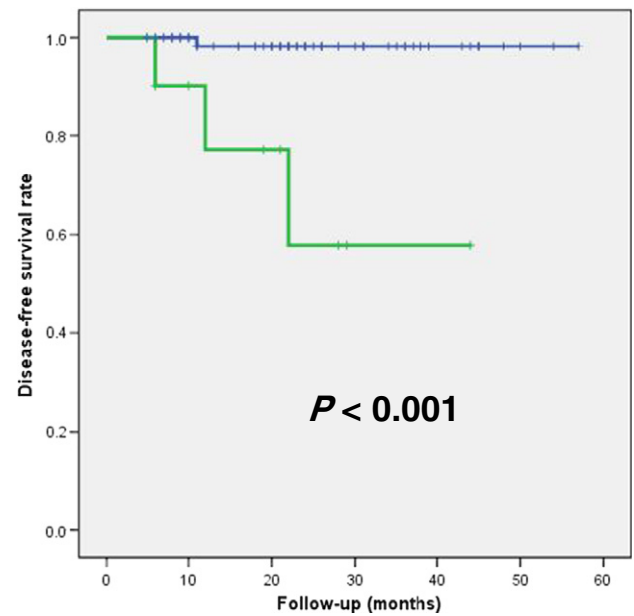
^{18}F-FDG uptake is heterogeneous throughout a tumor, and there are some factors known to contribute to IFH such as necrosis [21], cellular proliferation [22], blood flow [23], microvessel density [24], and hypoxia [25,26]. As the tumoral uptake of a radiopharmaceutical tracer is heterogeneously distributed in the tumor, it may be useful to quantify and follow up IFH throughout treatment period.

The risk of recurrence increased significantly with increased IFH. This result highlights the importance of the metabolic complexity of tumors and the possibility that IFH can be a novel and powerful prognostic biomarker of endometrial cancer. Although the clinical efficacy and benefit of more intensive surveillance strategy in patients with high IFH are not established, earlier detection of residual or metastatic lesions might influence the patients' outcome.

In the current study, we advocated the use of SUV-based automated contouring program to provide a reference for volume

Figure 3. Kaplan-Meier survival graph shows significantly different DFS between the groups categorized by intratumoral FDG uptake heterogeneity below (blue line) and above (green line) the optimal threshold (0.2651) (P < .001, log-rank test).

delineation, and voxels presenting a threshold of 40% SUV_{max} in the volume of interest within the contouring margin were incorporated to define the tumor volumes. Tumor delineation influences heterogeneity matrix, and we evaluated a threshold of 40% and a fixed isocontour at SUVs over 2.5, 3.0, 3.5, or 4.0. After comparison using ROC curve analysis, a threshold of 40% of SUV_{max} was chosen because it showed the highest value of the AUC in this study.

In the multivariate regression analyses, we included "nonsignificant borderline" parameters at univariate analysis because these are well-established risk factors of recurrence [27,28]. Although not included in the FIGO or TNM classifications, histological grade, the patient's age, tumor size, and lymphovascular space invasion (LVSI) have been identified as prognostic factors. Of interest, only the high IFH value (P = .007) was revealed as an independent risk factor of recurrence. Previous studies have underlined the high accuracy of ^{18}F-FDG PET/CT in detection of myometrial and cervical invasion and lymph node (LN) metastatic disease. However, although its prognostic value has been shown for advanced-stage endometrial cancer, its clinical use in preoperative staging in early-stage disease remains controversial [29,30]. In the current study, 68.1% of patients were FIGO stage I, and less than 30% of patients were in advanced stage, and such stage distribution might have influenced the result. A

Table 3. Multivariate Regression Analyses of Prognostic Factors DFS in Patients with Endometrial Cancer

Variables	Test for Progression-Free Survival	HR	95% CI	P
FIGO stage	III, IV vs I, II	5.375	0.317-91.266	.244
Tumor size		2.084	0.901-4.816	.086
IFH		2.545	1.468-8.674	.007

Table 4. Clinicopathological Characteristics of Patients Who Experienced Recurrence after Treatment for Endometrioid Endometrial Cancer (n = 4)

	Age (Year)	FIGO Stage	Tumor Grade	DFS (Months)	SUV_{max}	IFH
Patient 1	58	II	2	6	12.08	0.2873
Patient 2	60	IIIA	3	22	8.95	0.2732
Patient 3	38	IIIC	3	12	20.42	0.2658
Patient 4	45	IVB	2	11	19.52	0.2512

Table 5. Clinicopathological and PET/CT-Derived Characteristics of Patients without and with Recurrence (n = 72)

Variable	Without Recurrence (n = 68)		With Recurrence (n = 4)		P
	Mean	SD	Mean	SD	
Age (year)	53.412	10.315	50.250	10.532	.596
Tumor size	4.282	2.624	7.325	1.118	.004
SUV_{max}	13.660	8.762	15.243	5.618	.627
IFH	0.238	0.024	0.269	0.015	.018
DFS (months)	25.559	12.691	12.750	6.702	.022

larger study is warranted to further investigate the association between these parameters and prognosis.

Limitations to our study include relatively small group size and short follow-up. It was a retrospective study with a small number of patients and a short follow-up period without overall survival analysis. Also, there were only four patients with recurrence. Therefore, interpretation of the current study should be confined to short-term outcome focused on recurrence. The results in this study may not be generalizable to all patients with endometrial cancer because not all scans were available for IFH measurement and only measurable scans were included in the analysis. Also, this study may have spectrum bias because recruited patients had been selected as those with FDG PET/CT, and the subjects in this study may not represent the intended-use population. However, the current study is the first to demonstrate the prognostic value of preoperative IFH in patients with endometrioid endometrial cancer and suggests the clinical relevance of metabolic parameters. Second, histological confirmation of tumor heterogeneity or comparison with IFH observed in this study was not performed. Therefore, the extent and difference of histological features could not be investigated. Third, IFH applied in this study as a method to quantify heterogeneity might lose some information concerning spatial relationships within the tumor and might be confounded by high noise level. Partial volume effect can also cause distributions of measured intensities to appear more heterogeneous and may underestimate the SUV measure. In this aspect, we assumed that IFH may be less influenced by partial volume effect and can be a better candidate for prognostic parameter

Clinical implications of this study include possible stratification of endometrioid endometrial cancer recurrence before treatment. IFH helps identifying patients with an increased risk for disease recurrence, and these patients may benefit from an intensive therapy and follow-up strategy. The direct influence on prognosis using IFH needs to be investigated and verified in future studies.

The results of this study confirm the association between preoperative tumor ^{18}F-FDG uptake heterogeneity and a high tumor recurrence in endometrioid endometrial cancer. Current intuitive method showed statistically significant predictive capability for recurrence. Consequently, assessment of IFH may be included in routine preoperative ^{18}F-FDG PET/CT scans to identify those with a high risk of recurrence in patients with endometrioid endometrial cancer.

Compliance with Ethical Standards

Disclosure of Potential Conflict of Interest
Funding: none.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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