Prognostic Value of Metabolic Activity Measured by ^{18}F -FDG PET/CT in Patients with Advanced Endometrial Cancer

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Abstract

Purpose We evaluated the potential prognostic value of ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in patients with stage IIIC/IV endometrial cancer.

Methods Patients with stage IIIC/IV endometrial cancer who had undergone FDG PET/CT workup for staging were enrolled. Maximum standardized uptake values (SUV_{max}) measured from regions of interest (ROIs) of the primary tumor (SUV_t) and lymph nodes (SUV_n) were correlated with overall survival (OS). The SUV_n was defined as the highest SUV_{max} of the metastatic lymph nodes. Survival probability was assessed using the Kaplan-Meier method.

Results A total of 42 patients with a median age of 55.5 years (range 32–76 years) were included. Twenty-nine percent ($n=12$) of patients were premenopausal and 71 % ($n=30$) were postmenopausal. The average SUV_t was 12.9 (range 1.8–36.5), and the average SUV_n was 7.3 (range 2.0–22.5). Median follow-up time was 25.9 months (range 1–84 months). Using a SUV_t of 9.5 as a cutoff value, two groups with different rates were determined ($P=0.026$). In addition, patients with a low SUV_n had significantly better OS than those with a high SUV_n ($P=0.003$). Patients in the International Federation of Obstetrics and Gynecology (FIGO) stage IV group with SUV_t ≥ 9.5 or SUV_n ≥ 7.3 showed a significantly longer OS than the other groups.

Conclusions FDG uptake of primary endometrial cancer and lymph nodes might be a prognostic factor in advanced endometrial cancer. More aggressive therapy could be considered in patients with stage IV endometrial cancer and high SUV_t and/or high SUV_n.

Keywords Endometrial cancer · Prognosis · PET · Fluorodeoxyglucose

Introduction

Endometrial cancer is the most common cancer among gynecological malignancies and the fourth most common cancer in western countries [1]. Nearly 200,000 cases of endometrial cancer are diagnosed every year, contributing to significant morbidity and mortality in women worldwide [2]. The majority of endometrial cancer is diagnosed at an early stage and can be treated completely with a hysterectomy. Therefore, endometrial cancer detected at an early stage has a good prognosis, and the 5-year survival rate is over 80 % [1, 3]. Despite the overall favorable prognosis of endometrial cancer, advanced endometrial cancer shows substantial risk for recurrence and death. The 5-year survival in patients with a stage IV endometrial cancer rate is reported to be between 5 % and 15 % [4]. The prognostic factors for endometrial cancer are age, race, stage, grade, ploidy, depth of invasion, tumor size, receptor status, and cell type [5]. However, since some meaningful factors such as stage, tumor grade, and depth of tumor invasion are confirmed only after the staging procedure, it is necessary to identify a useful prognostic factor prior to surgery.

In recent years, positron emission tomography (PET) using 2-deoxy-2- ^{18}F fluorodeoxy-D-glucose (FDG) integrated with computed tomography (CT) has been introduced for the evaluation of metabolic activity with anatomic localization. Tumor glucose metabolism measured by FDG PET has been reported

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to be valuable in predicting the outcome of many cancers, such as head and neck squamous cell carcinoma [6–8], lymphoma [9–11], and esophageal [12] and lung cancers [13]. However, studies on the prognostic value of FDG PET in endometrial cancer are limited.

Although endometrial cancer with LN metastasis (stage IIIC and IV) has a poor prognosis, the added value of FDG PET/CT in predicting the prognosis of advanced endometrial cancer is not well elucidated. The purpose of this study was to evaluate the potential prognostic value of FDG PET/CT in patients with stage IIIC/IV endometrial cancer.

Materials and Methods

Patients

We retrospectively reviewed the medical records of all patients with endometrial cancer at a single center. The Institutional Review Board of our institute approved this study. Patients who received FDG PET/CT scans between 1 January 2005 and 31 July 2012 were included. A total of 253 patients underwent PET/CT scans before primary treatment. All patients underwent staging operations including transabdominal hysterectomy (TAH) and bilateral pelvic lymph node dissection (BPLD). Patient age ranged from 32 to 76 years (median age, 55.5 years). Age, menopausal status, obstetric history,

serum cancer antigen 125 (CA125) level and the presence of diabetes were recorded. All patients were confirmed to have endometrial cancer by endometrial biopsy performed through dilatation and curettage of the endometrium.

FDG PET/CT Protocol

A PET/CT system (Discovery LS; GE Healthcare, Milwaukee, WI, USA) was used for PET image acquisition. This system integrates a PET scanner (DSTe; GE Healthcare) with a multislice helical CT (16 slice; GE Healthcare). Subjects were instructed to fast for over 4 h before FDG injection. Image acquisition began 60 min after the injection of ~350 MBq of FDG. All FDG PET images were acquired in the supine position. During CT scan acquisition, free shallow breathing was recommended. For CT image acquisition, the following parameters were used: 140 kVp, 80 mAs, 0.5-s tube rotation, 4.25-mm section thickness, and 867-mm scan length with 22.5-s scan time. After CT image acquisition, the FDG PET scan was started with an emission time of 5 min per table position. Total PET acquisition time was 18 min with six table positions from the neck to the proximal thigh. CT data were used for attenuation correction. A diagnostic CT scan (scan field: 500 mm, increment of 3 mm, slice thickness 3.0 mm, pitch of 1.5 s per rotation, matrix 512×512, 120 KVp, 450 mAs) was performed after intravenous injection of 120 ml of contrast agent (2 cc/kg; Omnipaque, Amersham Health) by a dedicated PET/CT scanner. PET images were reconstructed using a standard two-dimensional iterative algorithm (ordered subset expectation maximization).

Image Evaluation and Data Analysis

Two nuclear medicine physicians interpreted all PET/CT images. Abnormal FDG uptake was defined as an FDG uptake that was higher than that of normal surrounding tissue. Maximum standardized uptake values (SUVmax) were used to

Table 1 Patient characteristics

Characteristics	Values
Age (years)	55.5 [32–76] ^a
BMI (kg/m ²)	24.3 [14.5–33.6] ^a
CA 125	271.3 [5.0–2548.3] ^a
Menopausal status	
Pre-menopausal	12 (29 %)
Post-menopausal	30 (71 %)
Parity	
0	7 (16.7 %)
1	5 (11.9 %)
2	13 (31.0 %)
3	9 (31.4 %)
≥4	8 (19 %)
FIGO stage	
IIIC1	14 (33.3 %)
IIIC2	15 (35.7 %)
IVA	4 (9.5 %)
IVB	9 (21.4 %)

BMI body mass index, FIGO International Federation of Obstetrics and Gynecology

^a Median [range]

Table 2 Pathology characteristics

Characteristics	Values (n)	Percent (%)
Histology		
Endometrioid carcinoma	26	61.9
Papillary serous carcinoma	9	21.4
Clear cell carcinoma	1	2.4
Carcinosarcoma ^a	6	14.3
Grade of tumor		
1	6	23.1
2	11	42.3
3	9	34.6

^a Formerly malignant mixed müllerian tumor, MMMT

Fig. 1 Kaplan-Meier survival analysis of overall survival by SUVmax of primary tumors and lymph nodes in advanced stage endometrial cancer patients. **a** With SUVt 9.5 as the cutoff value, the two patient groups show significantly different survival ($P=0.026$). **b** Survival differences between patients with SUVn<7.3 and SUVn≥7.3 were statistically significant ($P=0.003$)

quantitatively assess FDG activity. SUVmax was calculated as follows: $SUV_{max} = C_{max} \times TBW/IA$ [C_{max} : activity concentration in the voxel of highest metabolic activity (Bq/ml), TBW: total body weight (kg), IA: injected activity (kBq)]. A region of interest (ROI) was placed over the identified primary tumor and lymph nodes, and the SUVmax was calculated. Each ROI was placed over the FDG-avid lesion on the axial PET images. If accurate placement of the ROI on PET was deemed difficult because of little activity or no clearly discernible activity in the lesion, the CT component of the PET-CT study was used to place the ROI. The SUVmax in the endometrium (SUVt) and LNs (SUVn) was recorded for each ROI.

Surgical Staging

The staging procedure involved exploration of the abdominopelvic cavity, cytology exam of peritoneal washing fluid, suspicious lesion biopsy, hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and/or para-aortic lymph node dissection. Radical hysterectomy, omentectomy, or cytoreduction was performed if needed. Surgical staging was

performed according to the International Federation of Obstetrics and Gynecology (FIGO) staging system for endometrial cancer.

Statistical Analysis

SPSS for Windows (version 18.0) was used for statistical analysis. For survival analysis, overall survival (OS) was adopted as the primary endpoint. The OS time was measured from the date of the baseline PET/CT imaging to the date of cancer-related death. The Kaplan–Meier method was used to assess survival probability. The log-rank test was used to assess the survival difference between groups. The univariate Cox proportional hazards regression model was used to determine the utility of prognostic predictors. A P value of less than 0.05 was considered statistically significant.

Results

We examined 42 consecutive patients with FIGO stage IIIC ($n=29$) or IV ($n=13$) endometrial cancer. Of these 42 patients,

Fig. 2 Prognosis stratification by SUVmax and FIGO stage in patients with advanced stage endometrial cancer. **a** Kaplan-Meier survival graphs of overall survival according to the SUVmax of primary tumors and **b** metastatic lymph nodes

29 % ($n=12$) were premenopausal and 71 % ($n=30$) were postmenopausal. Table 1 summarizes the characteristics of the enrolled patients. The median period from the date of FDG PET/CT to the date of staging was 6.2 days (range 1–69 days). By histological exam, endometrioid adenocarcinoma was the most common type of endometrial cancer ($n=26$, 61.9 %), followed by papillary serous carcinoma ($n=9$, 21.4 %). The results of pathological diagnosis are shown in Table 2. The median follow-up period was 25.9 months (range 1–84 months), and 11 patients (26.2 %) died from endometrial cancer during the follow-up period.

In primary endometrial lesions, the average SUVmax of primary tumors was 12.9 (range 1.8–36.5). Since there was no discriminative cutoff value of SUVmax for prognosis, the subjects were divided into two groups: SUVt greater than 9.5 and SUVt lower than 9.5. The high SUVt group (SUVt>9.5) showed significantly poorer prognosis than the low SUVt group ($P=0.026$) (Fig. 1).

For lymph node evaluation, SUVn was defined as the highest SUVmax value among the metastatic lymph nodes in each patient. The average SUVn was 7.3 (range 2.0–22.5). The mean survival time of the 17 patients (40.0 %) with metastatic lymph nodes having an SUVmax<7.3 was 76.7 months (95 % CI), while the 25 patients (60.0 %) with SUVmax≥7.3 had a mean survival time of 40.2 months. Kaplan-Meier survival curves for the groups according to SUVmax are shown in Fig. 1. Survival was significantly different between patient groups with SUVn<7.3 and SUVn≥7.3 ($P=0.003$).

Kaplan-Meier curve analysis for different groups according to the FIGO stages and SUVmax was performed in a sub-study. Figure 2 shows the Kaplan-Meier curves of OS after baseline PET/CT according to FIGO stage and SUVmax. There was a statistically significant difference in OS between the patient groups that had FIGO stage IV with high SUVmax (SUVt≥9.5 or SUVn≥7.3) and the other groups in both cumulative survival and OS analyses.

The univariate evaluation of potential prognostic variables is shown in Table 3. Stage ($P<0.001$), SUVt ($P=0.027$), and SUVn ($P=0.003$) were determined to be significant prognostic factors by the Cox proportional hazards model.

Discussion

This study demonstrates the prognostic value of FDG PET/CT in advanced endometrial cancer. Glucose metabolic activities of both primary tumors and metastatic lymph nodes showed similar predictive value in assessing OS of patients with advanced endometrial cancer. Patients with stage IV and high SUVmax had significantly poorer rates of survival than the other groups.

Most cases (69 %) of endometrial cancer are diagnosed when the tumor is confined to the uterus, and the 5-year OS rate for these patients is 96 %. However, for patients with

Table 3 Univariate evaluation of potential prognostic factors with the Cox proportional hazards regression model

Potential prognostic factors	Values (<i>n</i>)	Hazard ratio	<i>P</i>
Histological type			
I: Endometrioid carcinoma	27	0.436	0.187
II: Nonendometrioid carcinoma	15	1	
Age			
62 or below	30	0.716	0.633
Above 62	12	1	
BMI			
<25	28	0.884	0.858
≥25	14	1	
Menopausal status			
Pre-menopause	12	0.878	0.849
Post-menopause	30	1	
Stage			
IIIC	29	0.071	<0.001
IV	13	1	
SUVt			
<9.5	30	0.027	0.027
≥9.5	12	1	
SUVn			
<7.3	17	0.138	0.003
≥7.3	25	1	
Serum CA125 level (U/ml)		1.001	0.385

BMI body mass index

advanced-stage endometrial cancer, the prognosis is grim: the 5-year OS rate was reported to be from 5 % to 15 % in patients with stage IV disease [14]. Our results suggest that FDG PET could select for patients with poorer prognosis prior to surgery who might benefit from more aggressive therapy.

Patients in this study were limited to those with stage IIIC or IV endometrial cancer. FIGO stage IIIC is defined as metastases to the pelvic and/or para-aortic LNs [15]. The LN status is an important prognostic factor because the survival rates of patients with metastatic LNs are significantly lower than in those without LN metastasis [16]. Furthermore, in the revised FIGO staging system for carcinoma of the endometrium [17], pelvic and para-aortic lymph node involvement in previous stage IIIC was separated because many studies suggested that the prognosis may be worse in para-aortic LN metastasis. That revision implies once again that LN metastasis is one of the most important prognostic factors in endometrial cancer. However, since tumor stage or LN status can only be confirmed after a staging operation, the introduction of a preoperative modality that predicts prognosis would be valuable in clinical decision making. A potential preoperative prognostic factor is glucose metabolism determined by FDG PET/CT.

FDG PET/CT has been a useful tool for cancer evaluation in a variety of malignancies including esophageal, lymphoma, lung, breast, colorectal, melanoma, and head and neck cancers.

In addition to providing information about diagnosis and staging, FDG PET/CT is used to predict clinical outcome [18]. The prognostic value of FDG PET/CT has been previously reported in several types of malignancies [6–8, 19]. Up to now, the clinical use of FDG PET/CT has been established in gynecological malignancies such as cervical, ovarian, and vulvar cancer. However, only a few studies [20, 21] have reported the prognostic value of FDG PET/CT in gynecological malignancies. To the best of our knowledge, this is the second report regarding the prognostic value of FDG PET/CT by semi-quantitatively measuring the SUVmax of primary tumors and LNs in endometrial cancer. Liu et al. [22] showed that pretreatment FDG PET/CT may be a valuable prognostic measure in stage IVB endometrial cancer. However, this study failed to show any significant meaning of the SUVmax of primary tumors or metastatic lesions. The cause of such a discrepancy might be the small sample size and limited patient group.

Our study showed that patients with low SUVmax values had a significantly longer OS than patients with high SUVmax values in advanced endometrial cancer. Regarding both the primary tumor lesions and metastatic lymph nodes, our results show that the SUVmax could determine different survival groups. Both SUVt and SUVn were significant prognostic factors for OS ($P=0.026$ and $P=0.003$, respectively). There was a statistically significant difference in OS between the patients who had FIGO stage IV with $SUVn \geq 7.3$ and the other groups. No significant difference was found between stage IIIC patients with high SUVmax and low SUVmax, probably due to the small number of patients and the relatively long survival rate. Patients with stage IV with lower SUVmax and stage III with lower SUVmax showed similar OS. Malignancies with high levels of glucose metabolism tended to have more aggressive behavior and poor prognosis. A strong correlation has been shown among FDG uptake, KI-67 expression and tumor grade for many solid tumors [7, 23–25]. Even among stage IV patients, prognosis differs significantly between the high and low FDG group in our study. Tumor aggressiveness measured by FDG PET might be as important as the stage for determining prognosis.

In the present study, patients with low SUVn had a significantly longer OS than those with high SUVn. Thus, a patient with a higher SUVn is expected to have poor survival, and more aggressive therapy should be considered. For these patients, additional treatment such as multimodality therapy, novel chemotherapy, or doublet regimens can be properly taken.

One limitation of this study is its retrospective, investigational design. Therefore, an inherent bias in patient selection related to the retrospective nature of the study might have been introduced. Another limitation is the small number of patients included in our study. Since most endometrial cancers are diagnosed at an early stage with uterine-confined tumors, advanced-stage disease comprises a small percentage of

endometrial cancer. Prospective studies with a larger scale are needed to further elucidate the prognostic role of FDG PET/CT in the preoperative evaluation of endometrial cancer. Another limitation is the intrinsic properties of the PET parameter. SUVmax represents radiation activity in a single pixel with the most intense FDG uptake and may not be the optimal quantitative parameter [26]. Further studies using alternative parameters that can represent metabolic/volumetric indices are needed.

In conclusion, FDG uptake in primary tumors and lymph nodes might be a prognostic factor in patients with FIGO stage IIIC/IV endometrial cancer.

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Conflict of Interest None.

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