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Prognostic value of ^{18}F-FDG PET/CT for identifying high- and low-risk endometrial cancer patients

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ABSTRACT

Objectives: To assess the usefulness of adding PET/CT as a preoperative test for determining the extent of endometrial cancer and discriminating low- and high-risk patients to identify candidates for surgical staging.

Material and methods: We retrospectively reviewed 86 patients with pathologically proven endometrial cancer who had undergone preoperative ^{18}F-FDG PET/CT. The prognostic relationships between PET/CT parameters and pathology reports were assessed.

Results: The SUV_{max} was significantly higher in patients with FIGO stage IB or higher compared with those with stage IA; for stage III–IV compared with stage I–II; and for patients with lymph node metastasis compared with those without lymph node metastasis. Using 6.70 as a cut-off for SUV_{max}, low-risk patients can be identified with a sensitivity of 92.9%.

Conclusions: PET/CT imaging can be used not only for determining malignancy and lymph node involvement but also for determining candidates for surgical staging with high sensitivity.

Key words: PET/CT, endometrial cancer, prognosis, SUV_{max}

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INTRODUCTION

Endometrial carcinoma is the most common gynaecological malignancy in developed countries, and after carcinoma of the uterine cervix, is the second most common gynaecological malignancy worldwide, with 319,600 new cases diagnosed in 2012 [1]. The prognosis for endometrial cancer is generally favourable because most patients have early-stage disease at the time of diagnosis [2]. The 5-year survival rate for endometrial cancer patients is ≥ 80% [3]. The main determinants of prognosis are disease stage, histological subtype, presence of lymph node metastasis, depth of myometrial invasion, and presence of cervical involvement [4]. The risk factors in advanced disease are less clear. The most widely accepted surgical staging system for endometrial cancer by the International Federation of Obstetrics and Gynaecology (FIGO) includes abdominal exploration, pelvic peritoneal cytology, hysterectomy, bilateral salpingo-oophorectomy, and pelvic and aortic selective lymphadenectomy. This system allows an accurate prediction of prognosis and assists in determining the optimal treatment for each patient. Given the invasive nature of the staging process, surgeons tend to rely on a detailed preoperative imaging evaluation to determine appropriate therapeutic management [5].

^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is an imaging method that can be used to obtain anatomic and metabolic data on cancer cells in various malignancies [6–8]. Several studies have examined the usefulness of ^{18}F-FDG PET/CT for determining the presence, stage, and aggressiveness of endometrial cancer [9, 10]. The standardised uptake value (SUV) is accepted as an indicator of tumour aggressiveness and a marker for metabolic changes in cancer tissues [11].

This study evaluated the use of SUV_{max} values and the diagnostic performance of FDG-PET in the preoperative evaluation of patients with endometrial cancer and in predicting recurrence in patients with endometrial cancer treated with surgery.

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MATERIAL AND METHODS

Patient characteristics

Patients diagnosed with endometrial cancer and referred to our Gynaecological Oncology Outpatient Clinic for preoperative assessment who underwent PET/CT as part of the preoperative evaluation were retrospectively enrolled in this study. The study protocol was approved by the institutional review board. Patients with a previous diagnosis of another malignancy, patients with postoperative follow-up for less than 1 year, and patients who did not undergo surgical staging for any reason were excluded from the study.

Following the preoperative evaluation, including PET/CT, all women underwent staging surgery including a total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic and para-aortic lymph node dissection. The pelvic lymphadenectomy included the bilateral external iliac, obturator, common iliac, and presacral nodes. The para-aortic lymphadenectomy included the nodal chains from the aortic bifurcation to the level of the left renal vein. The patients were staged according to the FIGO 2009 staging criteria [12]. The pathology was evaluated by experienced gynaecological pathologists at our institute who were blinded to the imaging information. The patients' demographic, clinical, and survival data were obtained from the hospital database and patient follow-up files.

Imaging technique

All patients underwent PET/CT in the 2 weeks before surgery. All patients fasted for at least 6 hours before the PET/CT imaging. ^{18}F-FDG (3.7 MBq/kg body weight) was administered antecubitally. After a 60–90-minute uptake period, whole-body PET/CT was performed.

The images were evaluated by a single experienced nuclear medicine physician. SUV_{max} was calculated using the equation SUV = A/(ID/BW), where A is the decay-corrected activity in tissue (in mCi per mL), ID is the injected dose of FDG (in mCi), and BW is the patient's body weight (in grams).

Statistical analysis

Descriptive statistics for continuous variables are presented as the median and range. The SUV_{max} distribution in relation to clinical covariates was determined using the Mann-Whitney *U*-test on the natural logarithm of the value. The comparison of SUV_{max} values between multiple subgroups were performed by oneway ANOVA test followed by Fisher's protected least significance difference test for all pairwise comparisons. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values of SUV_{max} for predicting clinical parameters. The area under the ROC curve (AUC) is presented as a measure of discrimination. In determining the optimal cut-off values, the Youden index was used. For all tests, *p*-values < 0.05 were considered significant. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) ver. 19.0 (SPSS, Chicago, IL).

RESULTS

We enrolled 92 eligible patients in this study. Six patients were excluded from the study either due to absence of a detailed final pathology result or because they were unable to undergo surgery due to comorbid illnesses. Ultimately, 86 patients with endometrial cancer were enrolled in the study. The mean patient age was 60.7 (range 39–84) years. The histopathological characteristics of the patients are summarised in Table 1. Of the patients, 74.5% (64 patients) had FIGO stage I and II disease. Overall, 46 of 86 (53.4%) patients had Grade I disease, and 77.9% (67/86) of these had the endometrioid subtype (Table 2).

The SUV_{max} was significantly higher in patients with FIGO stage IB or higher compared to stage IA patients, with median values of 8.0 vs. 11.4 ($p < 0.001$). There was also a significant difference between stage III–IV and stage I–II, with median values of 8.7 and 12.5, respectively ($p = 0.002$), and between patients with and without lymph node metastasis, with median values of 13.0 and 8.9, respectively ($p < 0.001$). Patients at low risk of extrauterine disease were identified using the Mayo Clinic criteria: grade 1–2 disease, tumour ≤ 2 cm, and myometrial invasion < 1/2. The SUV_{max} was significantly lower in the low-risk group compared with all other patients, with median values of 5.9 and 10.3, respectively ($p < 0.001$). In comparison, there were no significant differences in the SUV_{max} between FIGO grade 1–2 and FIGO grade 3, or between tumour diameters > 2 cm and < 2 cm ($p = 0.07$ and $p = 0.74$, respectively). There was also no significant difference between endometrioid and

Table 1. Histopathological characteristics of the patients

		Values	Percent
Age [years]	Mean (range)	60.7 (39–84)	
Tumour diameter	Mean (range)	3.41 (0.5–8)	
Myometrial invasion	None	10	11.6
	< 1/2	40	46.5
	> 1/2	36	41.9
Lymphovascular invasion	Positive	31	37
	Negative	55	62.8
Histological type	Endometrioid	67	77.9
	Mixed	8	9.3
	Clear	6	7.0
	Serous	3	3.5
	Other	2	2.4

Table 2. Clinicopathological characteristics of the patients

		Patients (n)	[%]	SUV_{max} median (range)
Disease stage	1A	38	44.2	8.0 (3.0–20.2)
	1B	20	23.3	9.5 (5.8–17.10)
	2	6	7.0	10.0 (7.7–14.3)
	3C	18	20.8	11.9 (3.9–18.7)
	4	4	4.7	9.7 (12.7–22.4)
Grade	I	46	53.5	8.6 (3.0–20.2)
	II	19	22.1	9.7 (4.5–16.7)
	III	18	20.9	11.1 (5.6–22.4)
Tumour diameter	< 2 cm	59	68.6	7.9 (3.0–22.4)
	> 2 cm	27	31.4	9.7 (3.1–18.4)
Myometrial invasion	None	10	11.6	8.1 (3.0–22.4)
	< 1/2	40	46.5	8.95 (3.1–20.2)
	> 1/2	36	41.9	10.3 (3.9–18.7)
Cervical stromal involvement	No	70	81.4	8.7 (3.0 – 22.4)
	Yes	16	18.6	10.7 (7.7– 18.4)
LN metastasis	Yes	20	23.3	13.0 (3.9–18.7)
	No	66	76.7	8.9 (3.0–22.4)
Risk assessment	Low	16	18.4	5.9 (3.0–11.5)
	High	70	80.5	10.3 (3.10–22.4)

Table 3. Association between clinicopathological characteristics and SUV_{max}

Variable	Number	SUV_{max} median (range)	p-value
FIGO stage			
IA	38	8.0 (3.0–20.2)	< 0.001
≥ IB	48	11.4 (3.9–22.4)	
FIGO stage			
I–II	64	8.7 (3.0–20.2)	0.002
III–IV	22	12.5 (3.9–22.4)	
Grade			
I	47	8.6 (3.0–20.2)	0.07
II–III	39	11.0 (4.5–22.4)	
Tumour diameter			
< 2 cm	27	7.9 (3.0–22.4)	0.74
> 2 cm	59	9.7 (3.1–18.4)	
LN metastasis			
Yes	20	13.0 (3.9–18.7)	< 0.001
No	66	8.9 (3.0–22.4)	
Subtype			
Endometrioid	67	9.7 (3.0–18.7)	0.983
Non-endometrioid	19	8.4 (3.1–22.4)	
Risk assessment			
Low*	16	5.9 (3.0–11.5)	< 0.001
High	70	10.3 (3.1–22.4)	

Mann-Whitney *U*-test
*Low risk: tumour diameter < 2 cm, grade I tumour, endometrial subtype, myometrial invasion ≤ 1/2

non-endometrioid subtypes, with median values of 9.7 and 8.4, respectively (p = 0.983) (Table 3).

The mean SUV_{max} values of the primary tumour with preoperative assessment of the primary endometrial cancer for the FIGO stage are listed in Table 4. For the FIGO stage, the mean SUV_{max} level for stage IB, III and IV was significantly higher than that for stage I (p = 0.027, 0.005, 0.000 respectively)

Figure 1 shows the ROC curves for discriminating low- and high-risk patients. The AUC was 0.830 [95% confidence interval (CI) 0.721–0.939]. Using 6.70 as a cut-off point, the sensitivity and specificity of SUV_{max} were 92.9% and 62.5%, respectively. Figure 2 shows the ROC curves for discriminating early- and advanced-stage patients. The AUC was 0.721 (95% CI 0.593–0.850). At a cut-off of 10.45, the sensitivity and specificity of SUV_{max} were 72.7% and 68.7%, respectively.

Table 4. Comparison between SUV_{max} values and FIGO (International Federation of Gynecology and Obstetrics) stage on preoperative assessment of primary endometrial cancer

Variable		SUV_{max}	
Stage	Number	Mean ± SE	p-value
IA	38	8.58 ± 0.63	
IB	20	10.9 ± 0.81	0.027
II	6	10.45 ± 0.91	0.258
III	18	11.63 ± 0.89	0.005
IV	4	17.67 ± 1.99	0.000

Oneway ANOVA

DISCUSSION

In endometrial cancer, a non-invasive, preoperative diagnostic method that evaluates the spread of disease would be useful for determining candidates for surgical staging while minimising costs [9]. Several preoperative imaging methods are used to determine the spread of disease in endometrial cancer, including ultrasonography, CT, and magnetic resonance imaging (MRI). However, all three techniques have some limitations [13]. The main prognostic factors in endometrial cancer are age, stage, histology, depth of myometrial invasion, cervical involvement, and lymph node metastasis [14]. Except age, all of the prognostic factors are evaluated after surgical staging. Several studies have evaluated the use of ^{18}F-FDG PET for staging in endometrial

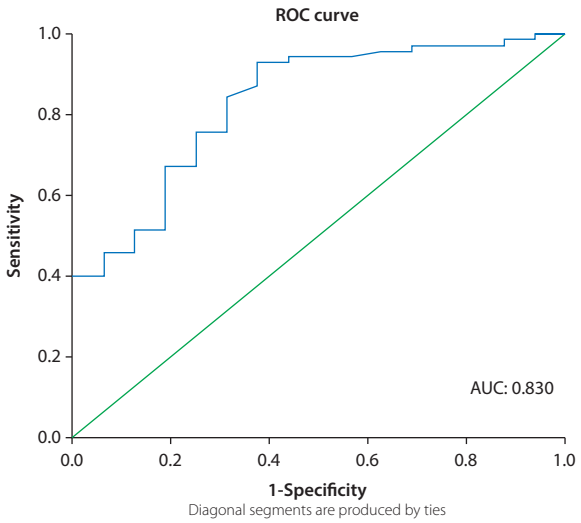

Figure 1. ROC curves for SUV_{max} for low- and high-risk patients with endometrial cancer

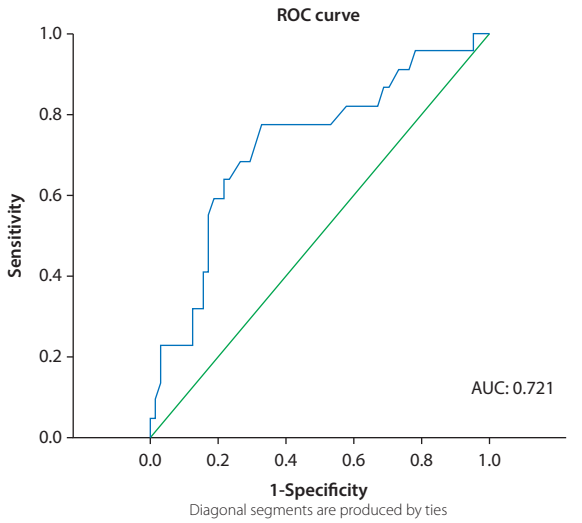

Figure 2. ROC curves for SUV_{max} for early and advanced stage in endometrial cancer

cancer patients. However, the main limitation of these studies and the meta-analysis of these studies is heterogenicity of the study population. In the current study, we wanted to evaluate the prognostic value of PET/CT imaging in endometrial cancer patients for determining low- and high-risk candidates for surgical staging. We believe that patients who need surgical staging can be identified with a non-invasive, preoperative imaging method.

SUV values are used to differentiate benign and malignant disease [15]. Endometrial sampling is a cost-effective method for detecting the primary tumour with high sensitivity and specificity [16]. A meta-analysis described the sensitivity of ^{18}F-FDG PET as suboptimal due to non-malignant physiological uptake of ^{18}F-FDG in the normal endometrium [15]. As our results show, there is a gradual increase in SUV_{max} with stage and grade. This finding supports the idea of an increase in metabolic activity with an increase in the extent of disease. The gradual increase in SUV_{max} can be used as an useful preoperative tool to stratified them to different surgical protocols based on PET/CT final results.

In 2013, the European Society for Medical Oncology (ESMO) separated endometrial cancer patients into three risk groups [17]. For the low-risk group, ESMO does not recommend lymphadenectomy based on the low probability of lymph node metastasis. The low sensitivity of PET/CT for determining lymph-node metastasis in endometrial cancer patients is the main shortcoming of this test as a diagnostic tool [15]. Omitting patients who need lymphadenectomy carries a risk of inadequate staging, leading to secondary lymphadenectomy or systematic adjuvant radiotherapy [18]. Discrepancy rates have been stated as up to 33% in some studies [19]. However, as shown in our study, the high sensitivity of PET/CT for discriminating high- and low-risk patients can be useful for determining candidates for lymphadenectomy. We believe that identifying low-risk patients preoperatively is important.

Like all other studies of the efficiency of PET/CT, our study has some limitations. The heterogeneity of the study group is one of the main limitations of our study. The relatively small study group is another weakness. Nevertheless, the promising result at differentiating low-risk patients preoperatively is a new aspect of PET/CT scanning.

CONCLUSIONS

PET/CT imaging can be used not only for determining malignancy or lymph node involvement but also for determining candidates for surgical staging. If our findings are confirmed by larger studies, PET imaging will become a more valuable preoperative diagnostic tool.

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