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Prognostic role of PET/CT in endometrial cancer

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ABSTRACT

Objectives: The present study evaluates the prognostic value of metabolic parameters related to the primary tumor identified in preoperative fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) scans in patients with endometrial cancer (EC).

Material and methods: This study included 120 patients with EC who underwent PET/CT in the preoperative period. The patients' age, maximum standardized uptake value (SUVmax), SUVmean, metabolic tumor volume (MTV) and the total lesion glycolysis (TLG) value of the primary tumor on PET/CT; as well as the stage, histological subtype, grade and size of the primary EC; the degree of myometrial invasion (MI) cervical invasion (CI), lymphovascular invasion (LVI), lymph node metastasis (LNM) and distant metastasis (DM) were all recorded. The relationship of these factors with progression-free survival (PFS) and overall survival (OS) was evaluated.

Results: The study included 120 patients with EC with a mean age of 62.3 ± 0.02 years. Of the total, 32 patients died around the time of the analysis and 38 patients showed disease progression. The mean OS was 32.7 ± 1.6 months and the mean PFS was 30.5 ± 2.8 months. No significant relationship was identified between the SUVmax, SUVmean, MTV, TLG values, patient age, tumor size, histology, grade and MI degree, and OS or PFS. Disease stage, LVI, CI, LNM and DM were identified as prognostic factors for OS and PFS.

Conclusions: The present study found no significant relationship between preoperative PET parameters in EC and OS and PFS, although prospective studies involving a larger number of patients are required.

Key words: endometrial cancer; survival; FDG PET/CT; SUVmax; MTV; TLG

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INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries [1]. The majority of patients are diagnosed in the early stage [2], and early-stage EC has a good prognosis with 5-year survival reaching 90% [3, 4]. That said, the rate of recurrence and the risk of death are high in advanced-stage EC [5] with the 5-year survival in the range of 20–26% in stage 4 EC [6]. Aside from disease stage, various other prognostic factors have also been described for EC, including histological type, grade, tumor size, myometrial invasion (MI) and lymph node metastasis (LNM) [7]. These prognostic factors can only be determined after extensive surgery [8], and so preoperative prognostic factors that are particulary important for patients who have comorbidities or for young patients who wish to preserve their fertility are sought. Also, some patients may survive even when faced with the same risk factors as those who do not survive, and additive prognostic factors are sought. F-18 fluorodeoxyglu-cose (FDG) positron emission tomography (PET)/computed tomography (CT) is a widely used imaging method in patients diagnosed with malignancy. PET parameters have been suggested to have a prognostic value in various cancer types such as lung cancer [9], esophageal cancer [10] and lymphoma [11–13]. There are, however, only a limited number of studies assessing the value of PET in determining the prognosis of EC.

The present study investigates the relationship between the metabolic parameters of the primary tumor on preoperative PET/CT in patients with EC and overall survival (OS) and progression-free survival (PFS). The study also investigates the prognostic value of certain clinicopathological factors in our patient population.

MATERIAL AND METHODS
Patients and follow-up

This retrospective study included 120 patients with a confirmed histopathological diagnosis of EC between April

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2010 and May 2014 who underwent preoperative F-18 FDG PET/CT in our department. None of the patients underwent therapy prior to PET/CT, and after PET/CT they underwent a total hysterectomy, bilateral salpingo-oophorectomy and pelvic (± paraaortic) lymphadenectomy. Patients received adjuvant therapy involving chemotherapy and/or radiotherapy according to the histological subtype, grade and stages noted by the International Federation of Gynecology and Obstetrics (FIGO) 2009. Progression-free patients were followed up every 3 months for the first two years, every 6 months for 2–5 years and once a year thereafter. As a matter of routine during the follow-up visits, medical histories were obtained, gynecological examinations were made, ultrasonographic data was recorded and serum cancer antigen 125 (CA125) levels were tested. Patients with suspected findings for recurrence underwent a pap smear, CT, MRI and/or PET/CT.

F-18 FDG PET/CT

Images were taken from the base of the skull to the upper thigh by a PHILIPS GEMINI TF 16 Slice PET/CT device. After at least 6 hours of fasting, 0.15 mCi/kg F-18 FDG was injected into patients with a blood glucose level of less than 200 mg/dl. The patients were allowed to rest in a quiet room for one hour after the injection, after which the images were acquired. PET images were acquired in 9–10 bed positions, for 1.8 min per bed position. The CT images were used for attenuation correction.

The 3D region of interest (ROI) was drawn for the primary tumor, and the maximum standardized uptake value (SUVmax) pertaining to the primary tumor in the region of interest was measured. SUVmean and metabolic tumor volume (MTV) were calculated, considering the recommended [14] 41% SUVmax as the threshold. The total lesion glycolysis (TLG) was calculated by multiplying the MTV by the SUVmean.

Survival data and statistical analysis

OS was defined as the time from the date of diagnosis to the date of death from EC, or the time of last observation. PFS was defined as the time from the date of diagnosis to the date of progression or death. Survival curves were created for the patients using the Kaplan-Meier method. SUVmax, SUVmean, MTV, TLG values and patient age were considered as a continuous variable. The relationship between patient age, PET parameters related to the primary tumor (SUVmax, SUVmean, MTV, TLG) and OS and PFS was evaluated using the Cox proportional hazard model. The difference in OS and PFS between the groups classified according to the FIGO stage, the histological subtype, grade, size, MI, cervical invasion (CI), lymphovascular invasion (LVI) and distant metastasis was evaluated using the log-rank test. A value of $p < 0.05$ was considered statistically significant in the analyses.

RESULTS
Patient characteristics

The study included 120 patients with a mean age of 62.3 ± 0.02 years (range 42–85 years) who had been diagnosed histopathologically with EC. According to the FIGO classification, 61 patients had stage 1, 26 had stage 2, five patients had stage 3 and 28 patients had stage 4 disease. Furthermore, 67 patients had an endometrioid histology and the remaining 53 patients had a non-endometrioid histology (mixed = 27, undifferentiated = 9, serous = 7, mucinous = 5, squamous = 4, clear cell = 1). Non-endometrioid subtypes were accepted as high-grade carcinoma. Eighteen of the patients with endometrioid carcinoma were grade 1, 35 were grade 2, and 14 were grade 3. The tumor size was ≥ 4 cm in 78 patients, MI was ≥ 50% in 69 patients, CI was positive in 29 patients, LVI was positive in 80 patients, pelvic or paraaortic LNM was positive in 13 patients and DM was positive in 17 patients.

Survival

Of the total sample, 32 died around the time of the analysis and 38 patients showed disease progression. The OS and PFS were 32.7 ± 1.6 months and 30.5 ± 2.8 months, respectively. When all patients are evaluated together in terms of the PET parameters of the primary tumor, the mean SUVmax was 17.3 ± 0.07, the mean SUVmean was 8.6 ± 0.2, the mean MTV was 30.8 ± 0.01 mL and the mean TLG was 295.2 ± 0.002 g. No significant relationship was identified between SUVmax, SUVmean, MTV, TLG values, patient age and OS and PFS ($p > 0.05$) (Tab. 1). Figures 1 and 2 present the PET parameters and survival data of the sample cases. There were no significant differences in terms of OS and PFS between the patients grouped according to tumor size (< 4 cm vs ≥ 4 cm), histology (endometrioid vs non-endometrioid), grade (grade1-2 vs grade 3) and MI degree (< 50% vs ≥ 50%) ($p > 0.05$). OS and PFS were lower in patients with advanced stage than in patients with early stage, in LVİ (+) patients than in LVI (-) patients, in CI (+) patients than in CI (-) patients, in LNM (+) patients than in LNM (-) patients, and in DM (+) patients than in DM (-) patients (Tab. 2).

Table 1. Survival analysis results of PET parameters and age

	Overall survival		Progression free survival	
	p	HR	p	HR
SUVmax	0.800	1.018	0.544	1.045
SUVmean	0.916	0.978	0.667	0.914
MTV	0.865	0.997	0.098	1.016
TLG	0.615	1.001	0.644	0.999
Age	0.820	1.007	0.414	1.022

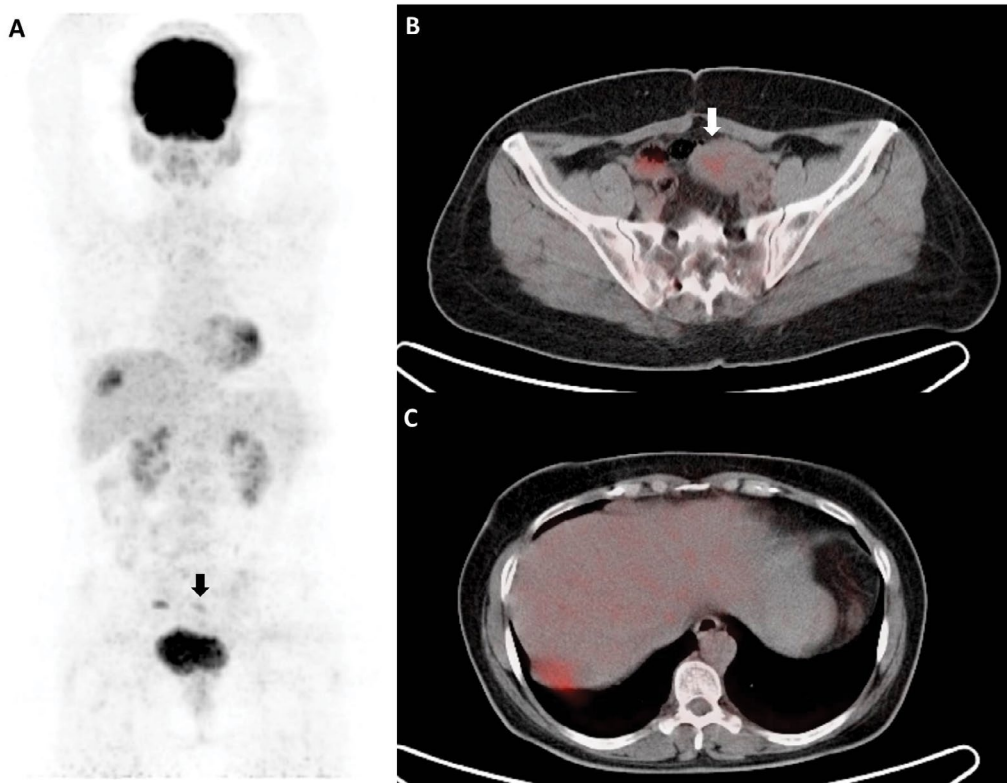SUVmax — maximum standardized uptake value; MTV — metabolic tumor volume; TLG — total lesion glycolysis

Figure 1. The MIP (A) and selected axial PET/CT (B, C) images of a 56-year-old patient with stage 4B undifferentiated endometrial cancer and a capsular implant in the liver are presented. Among the PET parameters of the primary tumor of the patient (A,B; arrows), SUVmax, SUVmean, MTV and TLG were found to be 3.8, 3, 1.2 mL and 3.6 g, respectively. The progression-free survival and overall survival of this patient were 6 months and 17 months, respectively
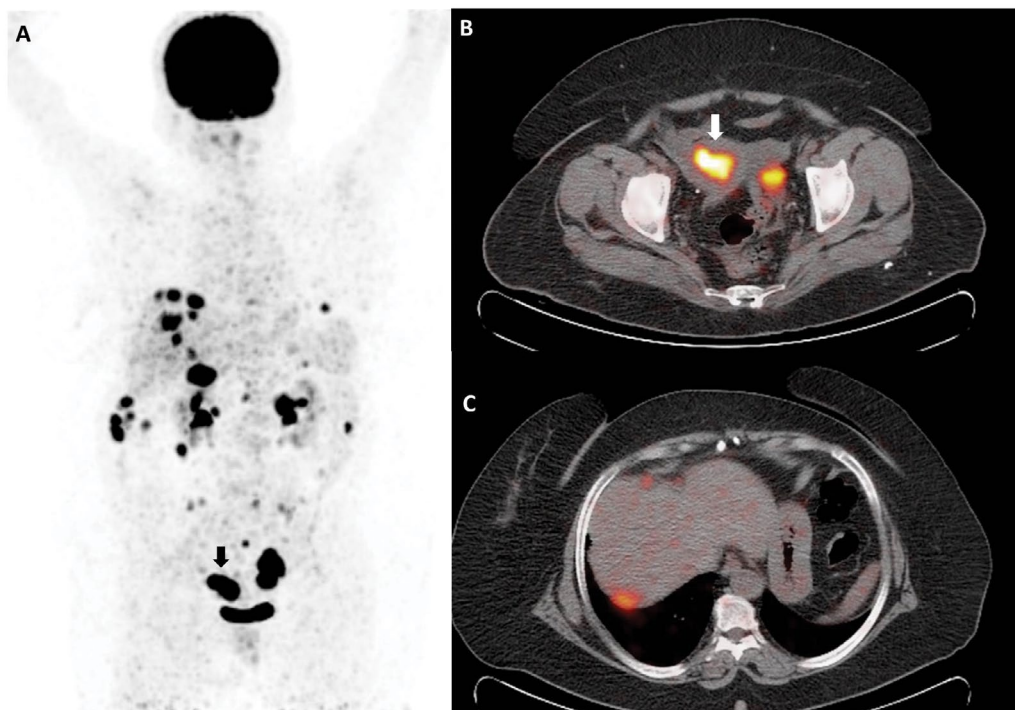

Figure 2. The MIP (A) and fusion (B, C) images of a 61-year-old patient with stage 4B mix endometrial cancer and a capsular implant in the liver are presented. The PET parameters of the primary tumor of the patient (A, B; arrows) were calculated as follows: SUVmax: 24.4, SUVmean: 8.5, MTV: 17.8 mL, and TLG: 151.3 g. The progression-free survival and overall survival of this patient were 8 months and 16 months, respectively

Table 2. Comparison of overall survival and progression free survival between the groups

	n	OS (mean ± SE, months)	p	PFS (mean ± SE, months)	p
Stage 1–2	87	43.7 ± 1.3	< 0.001*	42.7 ± 1.5	< 0.001*
Stage 3–4	33	21.9 ± 4.5		13.9 ± 4.1	
Tumor size < 4 cm	42	38.3 ± 3.0	0.881	36.6 ± 3.8	0.733
Tumor size ≥ 4cm	78	38.8 ± 2.2		36.0 ± 2.5	
LVI (–)	40	44.3 ± 2.0	0.027*	44.3 ± 2.0	0.007*
LVI (+)	80	36.0 ± 2.6		31.9 ± 3.0	
Endometroid	67	42.1 ± 2.1	0.156	41.1 ± 2.3	0.083
Nonendometroid	53	36.3 ± 2.9		32.1 ± 3.4	
Grade1–2	53	**42.8 ± 2.1**	0.190	**41.6 ± 2.3**	0.142
Grade 3	67	**36.7 ± 2.7**		**33.0 ± 3.1**	
MI < 50%	51	42.4 ± 1.9	0.163	41.0 ± 2.3	0.106
MI ≥ 50%	69	36.2 ± 3.0		32.7 ± 3.3	
CI (–)	91	42.6 ± 1.5	< 0.001*	41.6 ± 1.8	< 0.001*
CI (+)	29	25.8 ± 4.8		17.8 ± 4.6	
LNM (–)	107	41.0 ± 1.7	0.001*	39.3 ± 1.9	< 0.001*
LNM (+)	13	17.8 ± 4.8		9.1 ± 3.7	
DM (–)	103	40.9 ± 1.7	< 0.001*	39.2 ± 2.0	< 0.001*
DM (+)	17	17.4 ± 3.7		8.0 ± 2.2	

OS — overall survival; PFS — progression free survival; LVI — lymphovascular invasion; MI — myometrial invasion; CI — cervical invasion; LNM — lymph node metastasis; DM — distant metastasis; significant values (P < 0.05) are indicated with *

DISCUSSION

Most patients with EC are diagnosed in the early stage (FIGO 1–2) [6]. Five-year survival rates are 74–91% in early stage disease, 57–66% in stage 3 and 20–26% in stage 4 [6]. Aside from the disease stage, tumor histology, grade, depth of MI, LVI, presence of LNM and the patient's age can be counted among the clinicopathological prognostic factors [15]. Tumor size and various molecular factors have also been suggested to be of prognostic value in studies, although this is still under research [15]. However, survival may be different even in patients with the same risk factors. Furthermore, a large proportion of the known risk factors rely on staging during extensive surgery, which may be unnecessary in some patients with early-stage disease, and this is the subject of ongoing researches aimed at identifying preoperative noninvasive prognostic factors. FDG PET/CT is an effective imaging method that is used for initial diagnosis, staging, re-staging and evaluating response to therapy in a wide variety of cancers [16]. In the initial staging of endometrial cancer, PET/CT is recommended to detect extrauterine disease [17]. In addition, PET/CT has been shown to be useful in identifying candidates for surgical staging [18] and in determining post-operative recurrence [19]. But, only a limited number of studies evaluated the prognostic value of PET/CT in EC, and the results to date have been conflicting. In a study of 100 patients with stage 1–4 EC, Walentowicz-Sa-

dlecka et al. [8] identified significantly shorter OS in patients with a preoperative SUVmax ≥ 17.7 than in patients with a preoperative SUVmax of < 17.7. Another study involving 42 patients with EC (stage 3C–4) found significantly longer OS in patients with a low SUVmax of the primary tumor (< 9.5) or lymph node (< 7.3) than in patients with a higher SUVmax [5]. In a study of 84 patients with stage 1–4 EC by Shim et al. [7], preoperative MTV and TLG were identified as independent prognostic factors for PFS in EC, although no significant relationship was identified between PFS and SUVmax and SUVmean, or between OS and MTV and TLG values. In a study by Liu et al. [20] involving 15 patients with stage 4B EC, whole body MTV and whole body TLG were found to be significant prognostic factors for survival. The present study found no significant relationship between the SUVmax, SUVmean, MTV and TLG values of the primary tumor and OS and PFS. The heterogeneity of the study population in terms of such clinicopathological factors as stage, histology and grade is believed to be the cause of variety in the results. Furthermore, whole body measurements were carried out in the study by Liu et al., whereas the present study evaluated the PET parameters of the primary tumor. Such methodological differences may have also caused the differences in the results.

The present study identified FIGO stage, CI, LVI, and the presence of LNM and DM as prognostic factors for OS

and PFS, while age, tumor diameter, histology, grade, and MI were not found to be related to OS and PFS. Various risk classification systems have been developed to predict prognosis and to guide treatment of endometrial cancer. Risk factors such as FIGO stage, tumor histology, grade, MI and LVI are evaluated together in these classification systems [15]. However, in our study, we discussed the risk factors one by one. And so, the non-homogeneous distribution of other prognostic factors across the age groups and patients classified in terms of tumor histology, grade, diameter and MI degree, may have also resulted in the difference in the current findings. For example, LNM was mostly present in patients aged < 62 years. In a meta-analysis including 14 studies (672 patients), complete cytoreduction to no gross residual disease for patients with advanced or recurrent endometrial cancer was found to be associated with superior overall survival outcome [21]. However, we did not evaluate the presence of post-treatment residual tumor. Furthermore, although all patients in the present study underwent surgery, post-operative treatments were not standard. Differences in the treatment management may have contributed to current results. In addition, some micrometastases may not be detected during surgery or by PET/CT. The presence of undetectable micrometastasis may also have affected prognosis. AlHilli et al. [22] declared a relationship between tumor diameter and survival. In that study, 2 cm was utilized for the cut-off value of the tumor size [22]. But we used a threshold of 4 cm that may have caused us to find a different result.

In the present study, 5-year survival rates were not evaluated and there were limitations such as relatively short follow-up period and retrospective design.

CONCLUCIONS

No significant relationship was found between PET parameters and OS and PFS, and so prospective studies involving a larger number of patients with more homogeneous groups are needed.

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