Original Article

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Prognostic Importance of ^{18}F-FDG Positron Emission Tomography in Uterine Cervical Cancer

Uterin Serviks Kanserinde ^{18}F-FDG Pozitron Emisyon Tomografisinin Prognostik Önemi

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Abstract

Objectives: The aim of this study was to evaluate the prognostic value of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) in the uterine cervix cancer patients.

Methods: Thirty-two women (mean age: 52.7±12.6) who underwent ^{18}F-FDG PET/CT for staging of uterine cervix cancer were retrospectively recruited for the study. Maximum standardized uptake value (SUV_{max}), SUV_{mean}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) for primary tumors, lymph nodes, and distant metastases were calculated from ^{18}F-FDG PET/CT images using the 40% threshold. Patients were divided into groups according to the presence of pelvic and para-aortic lymph node involvement on ^{18}F-FDG PET/CT images. Life tables and Kaplan-Meier analyses were performed to compare the mean survival times of the different groups.

Results: Primary tumor of 27 (84%) patients were ^{18}F-FDG avid. The median SUV_{max}, SUV_{mean}, MTV, and TLG of the primary tumors were 12.4, 6.1, 13.2 cm^3 and 87.8 g/mL x cm^3 respectively. Pathological uptake was detected in pelvic 14 (44%) patients and in paraaortic lymph nodes in 3 (10%) para-aortic lymph nodes. The median whole-body MTV and TLG were 21.7 cm^3 and 91.1 g/mL x cm^3. Disease progression was detected in 7 (22%) patients within a median follow-up period of 20.9 (minimum-maximum: 3-82) months. The only significant PET parameter to predict progression-free survival was SUV_{max} in the primary tumor (p=0.038). During follow-up period 8 patients died. SUV_{max} (p=0.007), MTV (p=0.036), TLG (p=0.001) of primary tumor, presence of pathological uptake on pelvic or paraaortic lymph nodes (p=0.015), whole-body MTV (p=0.047) and whole-body TLG (p=0.001) were found statistically significant PET parameters to predict overall survival.

Conclusion: Metabolic parameters of primary tumors derived from ^{18}F-FDG PET/CT images have prognostic importance for patients with uterine cervical carcinoma. In patients with metastatic disease, higher whole-body MTV and TLG are also associated with poor prognosis.

Keywords: Uterine cervix cancer, ^{18}F-FDG PET/CT, prognosis

Öz

Amaç: Bu çalışmanın amacı uterin serviks kanserli hastalarda ^{18}F-florodeoksiglukoz (^{18}F-FDG) pozitron emisyon tomografisi/bilgisayarlı tomografinin (PET/BT) prognostik değerinin araştırılmasıdır.

Yöntem: Uterin serviks kanseri evrelemesi için ^{18}F-FDG PET/BT yapılan 32 kadın (ortalama yaş: 52,7±12,6) retrospektif olarak çalışmaya dahil edildi. Primer tümörler, lenf nodları ve uzak metastazlar için maksimum standardize tutulum değeri (SUV_{maks}), SUV_{ort}, metabolik tümör hacmi

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(MTV) ve toplam lezyon glikolizi (TLG) parametreleri, ^{18}F-FDG PET/BT görüntülerinden %40 eşik değerine göre hesaplandı. Hastalar ^{18}F-FDG PET/BT görüntülerinde pelvik ve paraaortik lenf nodu tutulumu varlığına göre gruplara ayrıldı. Farklı grupların ortalama sağkalım sürelerinin karşılaştırılması için sağkalım ve Kaplan-Meier analizleri yapıldı.

Bulgular: Hastaların 27'sinde (%84) primer tümörde ^{18}F-FDG tutulumu gözlendi. Primer lezyonların SUV_{maks}, SUV_{ort}, MTV ve TLG ortanca değerleri sırasıyla 12,4, 6,1, 13,2 cm^3 ve 87,8 gr/mL x cm^3 olarak hesaplandı. Hastaların 14'ünde (%44) pelvik ve 3'ünde (%10) paraaortik lenf nodlarında patolojik tutulum tespit edildi. Tüm vücut MTV ve TLG için ortanca değerler 21,7 cm^3 ve 91,1 gr/mL x cm^3 olarak hesaplandı. Ayrıca 20,9 aylık medyan takip (minimum-maksimum: 3-82) süresinde 7 (%22) hastada progresyon izlendi. Progresyonsuz sağkalımı öngören tek anlamlı parametere primer lezyonun SUV_{maks}'ı olarak bulundu (p=0,038). Takip süresi boyunca 8 hasta eksitus oldu. Genel sağkalımı öngören parametreler ise primer lezyonun SUV_{maks}'ı (p=0,007), MTV'si (p=0,036), TLG'si (p=0,001), pelvik veya paraaortik lenf nodlarında patolojik tutulum varlığı (p=0,015), tüm vücut MTV (p=0,047) ve tüm vücut TLG (p=0,001) olarak bulundu.

Sonuç: Uterin servikal karsinom hastalarında ^{18}F-FDG PET/BT görüntülerinden elde edilen primer tümörün metabolik parametreleri prognostik öneme sahiptir. Metastatik hastalık durumunda daha yüksek toplam MTV ve TLG değerleri de kötü prognoz ile ilişkilidir.

Anahtar kelimeler: Uterin serviks kanseri, ^{18}F-FDG PET/BT, prognoz

Introduction

Uterine cervical cancer is one of the most common cancers and the fourth leading cause of cancer-related death in women (1). Recurrence rates are changing based on the International Federation of Gynecology and Obstetrics (FIGO) staging range between 11% and 64% (2). In cases of recurrent disease, different treatment options are available according to disease spread. If local disease recurrence occurs, radical retreatment can be performed. However, this widespread disease can be treated with only systemic chemotherapy or supportive care (3).

FIGO stage, tumor size, presence of parametrial invasion, and presence of lymph node metastasis are well-known prognostic factors (4,5,6). Although they are not mandatory in disease staging, the role of non-invasive imaging modalities in the management of uterine cervical cancer is increasing (7,8,9). As a combined imaging technique, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been proven to be a valuable tool in several aspects of uterine cervical cancer (10,11,12). Although maximum standardized uptake value (SUV_{max}) is the most widely used semiquantitative parameter for PET/CT evaluation, SUV_{max} has limitations, such as it is susceptible to noise and does not represent the entire tumor. For this reason, volume-based parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), are utilized to predict the biological behavior of tumors. They have been shown to be effective in prognostic prediction in several solid tumors (13,14). However, their role in patients with uterine cervical cancer is not yet well-established. For this reason, in this study, we aimed to evaluate the prognostic value of ^{18}F-FDG PET/CT in the uterine cervix cancer patients.

Materials and Methods

Patient Population

Thirty-two women (mean age: 52.7±12.6) who underwent ^{18}F-FDG PET/CT for the staging of uterine cervix cancer were retrospectively recruited for the study. All patients had pathologically proven uterine cervix cancer diagnosis. Patients were enrolled consecutively from January 2012 to September 2022. Informed consent was obtained from the patients for the scan and for accessing their hospital records. After PET/CT, patients were treated according to disease stage.

The Human Research Ethics Committee of Ankara University Faculty of Medicine approved this study (decision no.: İ01-68-24, date: 06.02.2024).

^{18}F-FDG PET/CT Imaging

^{18}F-FDG PET/CT imaging was performed using a GE Discovery 710 PET/CT scanner (GE Medical Systems, Milwaukee, USA) according to published guidelines for tumor imaging with PET/CT (15). Patients fasted at least 6 h before the examination, and their glucose levels were assessed. After 5.5 MBq/kg ^{18}F-FDG injection, to clear background activity and reduce radiation exposure, patients were subjected to imaging after resting for 60 min in a quiet lead-lined room on semi-recumbent chairs. PET images were acquired for 4 min per bed position. The following parameters were used to obtain a low-dose CT scan before the PET scan. 140 kV, 70 mA, tube rotation time of 0.5 s per rotation, pitch of 6, and slice thickness of 5 mm.

Follow-up

Follow-up data were obtained from medical records, and surveillance was performed clinically, with aging [CT and/or magnetic resonance imaging (MRI) and/or ^{18}F-FDG PET-CT] performed once a year, with a maximum (max) follow-

up period of up to 10 years. Progression was defined as the occurrence of cancer-related death, new lesions observed on follow-up imaging, or progression in the size and/or metabolic activity of existing lesions. Progression-free survival (PFS) was calculated from the day of PET/CT examination until disease progression was detected or the end of the follow-up period if no progression was detected. Overall survival (OS) was calculated from the day of PET/CT examination until death or end of the follow-up period if the patient was alive.

Image and Data Analysis

Reconstructed images were displayed as max intensity projection images, PET, CT, and fused PET/CT images in the axial, coronal, and sagittal planes re-evaluated retrospectively on a dedicated workstation (Advance Workstation 4.7 GE Medical Systems, Milwaukee, USA) for the presence of pathological uptake on primary tumors, pelvic lymph nodes, and distant organs by two experienced nuclear medicine specialists by consensus. SUV_{max}, SUV_{mean}, MTV, and TLG for primary tumors, lymph nodes, and distant metastases were calculated from ^{18}F-FDG PET/CT images by the 40% threshold. In addition, whole-body MTV and TLG values were calculated by summing the MTV and TLG values for the primary tumor, lymph node, and distant organ metastases. Patients were divided into groups according to the presence of pelvic and para-aortic lymph node involvement on ^{18}F-FDG PET/CT images.

Statistical Analysis

Baseline clinical and demographic information on the patients was analyzed using descriptive statistics. Categorical data are presented as frequencies, whereas continuous variables are presented as mean ± standard deviation or median (interquartile range). Statistical analysis was performed using the commercially available software package SPSS 28.0. Normalcy was assessed using the Kolmogorov-Smirnov test. For non-normally distributed data, the Mann-Whitney U test, Kruskal-Wallis test, and Spearman rank test were used when appropriate. For normally distributed data, ANOVA with post-hoc Bonferroni correction, the student t-tests and the Pearson correlation test were used when appropriate. Life Tables and Kaplan-Meier analyses were performed to compare the mean survival times of the different groups. The log-rank method was used for this comparison. Statistical significance was defined as a p-value ≤0.05.

Results

In total, 32 women with mean age: 52.7±12.6 were included to the analysis. The majority of patients (75%) had the squamous cell subtype, and the rest had adenocarcinoma. Following PET/CT imaging, 19 patients (60%) underwent total abdominal hysterectomy and bilateral salpingoophorectomy +/- pelvic lymph node dissection, 21 (65%) received radiation therapy, and 17 (53%) received chemotherapy. Patients were followed up for a mean of 52 months [minimum (min)- maximum (max): 3-133].

Primary tumors of 27 (84%) patients were ^{18}F-FDG-avid. The median SUV_{max}, SUV_{mean}, MTV, and TLG of the primary tumors were 12.4, 6.1, 13.2 cm^3 and 87.8 g/mL x cm^3 respectively. Pathological uptake was detected in pelvic lymph nodes of 14 (44%) patients and in paraaortic lymph nodes in 3 (10%) para-aortic lymph nodes. Distant organ metastasis was detected in 7 (21%) patients. Two (6%) patients had peritoneal lymph node metastasis, 1 (%3) patient had surrenal gland metastasis, and 4 (13%) patients had distant lymph node metastasis. The median whole-body MTV and TLG were 21.7 cm^3 and 91.1 g/mL x cm^3.

Disease progression was detected in 7 (22%) patients within a median follow-up period of 20.9 (min-max: 3-82) months. The only significant PET parameter to predict PFS was SUV_{max} in the primary tumor. While patients who had a primary tumor with SUV_{max} higher than or equal to 12.4 had median 66.2±13.6 months PFS, patients who have lower than 12.4 had 116.1±8.5 months (p=0.038).

During the follow-up period 8 patients died. MTV (118.8±9.1 vs. 78.8±14.1 months, p=0.036), TLG (126.8±6.4 vs. 47.4±6.8 months, p=0.001), and SUV_{max} (125.6±7.9 vs. 60.9±10.1 months, p=0.007) values of the primary tumor, presence of pathological uptake on pelvic or para-aortic lymph nodes (111.0±8.2 vs. 72.8±17.2 months, p=0.015), whole-body MTV (118.8±9.1 vs. 80.4±14.0 months, p=0.047), and whole-body TLG (126.8±6.4 vs. 47.4±6.8 months, p=0.001) were found to be statistically significant PET parameters to predict OS. Survival analyses are detailed in Table 1. Examples of patients showing the relationship between PET/CT parameters and prognosis are shown in Figures 1 and 2. Survival curves of the different patient groups are presented in Figure 3. OS was better in patients without distant organ metastases, but the difference was not statistically significant (106.2 vs. 47.4 months, p=0.11).

Discussion

Because of the limitations of ^{18}F-FDG PET/CT in the evaluation of primary tumors associated with myometrial and parametrial invasion, it is recommended for the assessment of pelvic lymph nodes and distant metastases in uterine

Table 1. Details of survival data of different patient groups			
Parameter	**Median OS (months)**	**SD**	**p-value**
MTV of primary tumor			
≥13.2	78.8	14.2	0.036
<13.2	118.9	9.1	
TLG of primary tumor			
≥87.8	47.4	6.8	0.001
<87.8	126.8	6.4	
SUV_{max} of primary tumor			
≥12.4	60.9	10.1	0.007
<12.4	125.6	7.9	
Presence of lymph node metastasis			
Present	72.8	17.2	0.015
Absent	111.0	8.2	
Whole-body MTV			
≥21.7	80.4	9.1	0.047
<21.7	118.8	14.0	
Whole-body TLG			
≥91.1	47.2	6.8	0.001
<91.1	126.8	6.4	

SUV: Standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, OS: Overall survival, SD: Standard deviation

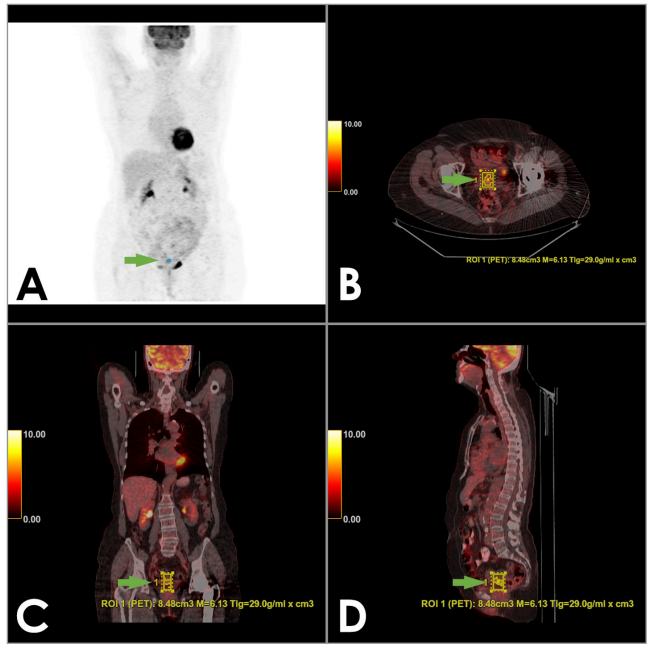

Figure 1. Maximum intensity projection PET (A), fused transaxial (B), coronal (C) and sagittal (D) PET/CT images of a 70 year-old woman with squamous cell uterine cervix carcinoma. She had a primary tumor with SUV_{max}: 6.13, MTV: 8.48 cm^3 and TLG: 29.0 g/mL x cm^3 without lymph node metastasis. After PET/CT imaging, she underwent TAH + BSO following by adjuvant chemo-radiation therapy. She has been followed-up for 46 months with no recurrent disease and still alive

PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, TAH + BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy, ROI: Region of interest

cervical cancer staging. However, metabolic parameters of primary tumors are known to have a prognostic role by providing information about the biological behavior of tumors in several solid tumors (16,17). Because of the rare incidence of uterine cervical cancer compared with other gynecological malignancies, the prognostic role of the metabolic parameters of the primary tumor assessed using ^{18}F-FDG PET/CT is needed.

In this study, we investigated the prognostic role of ^{18}F-FDG PET/CT in patients with uterine cervical carcinoma in terms of OS and PFS. Volume-based parameters, such as MTV and TLG, have been identified as predictors of PFS in patients with uterine cervical cancer in previous analyses (18,19). In a recent study, Markus et al. (20) showed that MTV and TLG were more effective in predicting the survival of patients with cervical cancer. In our study, we showed that primary tumor and whole-body MTV and TLG values were effective in predicting the OS. In addition, the SUV_{max} of the primary tumor and the presence of para-aortic-pelvic lymph nodes were found to be effective in predicting OS in our study. Budak et al. (21) showed that TLG and MTV were associated with PFS. In contrast to these findings in our analysis, only the SUV_{max} value of the primary tumor was found to be effective in predicting PFS for the prediction. The limited number of included patients and different treatment strategies could be the reason for this difference in our group.

Despite these limitations in predicting OS, beyond SUV_{max}, MTV, and TLG were found to be significant factors. It is predicted that volume-based metabolic parameters have great potential for disease progression in uterine cervical cancer due to the heterogeneous nature of uterine cervical tumors due to the intra-tumoral variability of hypoxia, cellular proliferation, and blood flow; ^{18}F-FDG uptake of the tumor is generally heterogeneous (5). Thus, SUV may not reflect exact metabolic activity of the entire tumor. The MTV reflects the volume of the area with higher uptake than the SUV_{max} threshold. The prognostic importance of TLG was not a surprise due to the known prognostic role of the tumor itself. TLG is calculated by multiplying MTV and SUV_{mean}, and it is hypothesized as a marker for the biological behavior of the tumor by providing information for tumor volume and glycolytic activity together. Despite the limited number of included patients, our analysis supported the hypothesis.

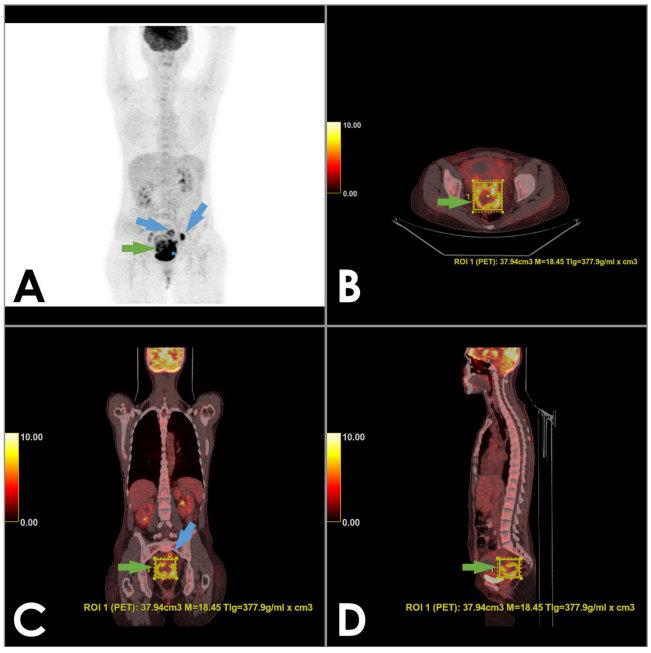

Figure 2. Maximum intensity projection (MIP) PET (A), fused transaxial (B), coronal (C) and sagittal (D) PET/CT images of a 33 year-old woman with squamous cell uterine cervix carcinoma. She had a primary tumor with SUV_{max}: 18.45, MTV: 37.94 cm^3 and TLG: 377.9 g/mL x cm^3 with pelvic lymph node metastases. After PET/CT imaging, she underwent TAH + BSO following by adjuvant chemo-radiation therapy. She had recurrent disease at the 7th month and died at the 12th month after PET/CT

PET: Positron emission tomography, CT: Computed tomography, SUV_{max}: Maximum standardized uptake value, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, TAH + BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy, ROI: Region of interest

The presence of lymph node metastases is a well-known prognostic factor in the uterine cervical cancer patients (22,23). Assessment of lymph node involvement using different imaging modalities showed a higher overall diagnostic performance of PET/CT in the per-patient and region- or node-based analyses. The sensitivity was 82%, 50%, and 56%, and the specificity was 95%, 90%, and 91% for PET/CT, CT, and MRI, respectively (23). In addition to the high diagnostic performance of ^{18}F-FDG PET/CT in the detection of lymph node metastases, the presence of pathological uptake in pelvic and para-aortic lymph nodes was found to be a significant prognostic factor in our analysis.

An advantage of ^{18}F-FDG PET/CT is that it is a whole-body imaging method. With this advantage, distant organ metastases were detected in 7 (22%) patients. To assess the prognostic importance of ^{18}F-FDG-positive distant organ metastasis, we additionally evaluated the prognostic role of whole-body MTV and TLG. Patients with a whole-body MTV higher than 21.7 cm^3 and TLG >91.1 gr/mL x cm^3 were associated with shorter OS times than those without.

In a study investigating the effect of PET/MRI on survival in patients with cervical cancer, the SUV_{max}, MTV, and TLG values of the primary tumor were associated with PFS, but the SUV_{max} value was an independent predictor of PFS. It was also reported that the minimum apparent diffusion coefficient value was an independent predictor of OS. No significant correlation was found between MTV TLG and SUV_{max} and OS. This result was thought to be due to the small number of patients. In our study, we observed that

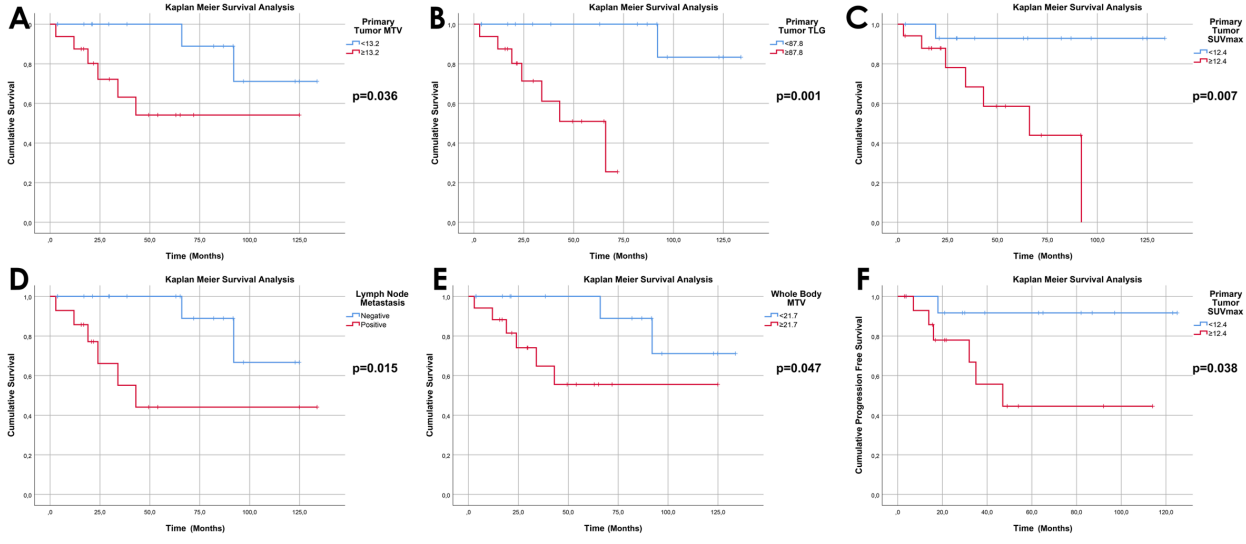

Figure 3. Kaplan-Meier survival curves of different subgroups of patients. Association of primary tumor MTV, TLG, SUV_{max} values with overall survival (A, B, C), Association of the presence of pelvic or paraaortic pathologic lymph nodes with overall survival (D), Association of whole-body MTV value with overall survival (E), Association of primary tumor SUV_{max} with progression-free survival (F). P-values were calculated with the long rank method
MTV: Metabolic tumor volume, TLG: Total lesion glycolysis, SUV_{max}: Maximum standardized uptake value

OS and PFS were lower in patients with higher SUV_{max} values for the primary tumor (24).

There are limitations to this study. First, it has a retrospective design and a limited number of patients. Second, the disease stages of the included patients were heterogeneous, and treatment strategies were not standardized. However, owing to its limitations, this study may contribute to the definition of the prognostic role of metabolic PET parameters for the prediction of uterine cervical cancer patients by considering the existence of limited data in this area.

Conclusion

Metabolic parameters of primary tumors derived from ^{18}F-FDG PET/CT images have prognostic importance for patients with uterine cervical carcinoma. In patients with metastatic disease, higher whole-body MTV and TLG are also associated with poor prognosis.

Ethics

Ethics Committee Approval: The Human Research Ethics Committee of Ankara University Faculty of Medicine approved this study (decision no.: İ01-68-24, date: 06.02.2024).

Informed Consent: Patient consent was obtained.

Authorship Contributions

Surgical and Medical Practices: Ç.S., M.H.B., M.A., E.D., S.T., N.Ö.K., F.O., Concept: M.A., B.D., E.D., Design: Ç.S., M.H.B., M.A., B.D., E.D., Data Collection or Processing: Ç.S., M.H.B., M.A., B.D., Analysis or Interpretation: Ç.S., M.H.B., B.D., E.D., Literature Search: Ç.S., M.H.B., M.A., B.D., E.D., Writing: Ç.S., M.H.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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