Zeynep Kamil Med J 2024;55(3):128–133
DOI: 10.14744/zkmj.2024.79664

ORIGINAL ARTICLE

Prediction of prognostic factors in endometrial cancer with PET-CT imaging

[1]Varol GÜLSEREN
[2]Mehmet DOLANBAY
[1]Mine DAĞGEZ
[3]Ümmühan ABDÜLREZZAK
[2]Fulya ÇAĞLI
[3]Ahmet TUTUŞ
[1]Bülent ÖZÇELİK
[1]Serdar SERİN
[4]Kemal GÜNGÖRDÜK

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[2]Department of Obstetrics and Gynecology, Erciyes University Faculty of Medicine, Kayseri, Turkey

[3]Department of Nuclear Medicine, Erciyes University Faculty of Medicine, Kayseri, Turkey

[4]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Mugla Sitki Kocman University Faculty of Medicine, Mugla, Turkey

ORCID ID
VG : 0000-0002-0779-8305
MD : 0000-0002-8332-1568
MDa : 0000-0001-5266-9652
ÜA : 0000-0002-7100-1866
FÇ : 0000-0002-6492-3379
AT : 0000-0002-6643-6363
BÖ : 0000-0003-3257-8088
SS : 0000-0002-7306-1184
KG : 0000-0002-2325-1756

ABSTRACT

Objective: The aim of our study is to evaluate the lymphovascular space involvement (LVSI) status using preoperative fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) imaging.

Material and Methods: This retrospective study was based on a review of the records of patients who were diagnosed with endometrial cancer (EC) and underwent hysterectomy between January 2014 and 2021. The thickness, volume of the uterine lesion, and its standardized uptake value (SUV_{max}) as obtained using 18F-FDG PET-CT and pathology results of hysterectomy specimens were recorded.

Results: All 151 patients included in the study had endometrioid-type cancer. Recurrence was observed in 22 (14.6%) patients. To predict LVSI, deep myometrial invasion, cervical involvement, and lymph node (LN) metastasis preoperatively, ideal SUV_{max} values in PET-CT were analyzed according to receiver operating characteristic (ROC) analysis. Deep myometrial invasion, cervical involvement, LVSI, and LN metastasis, which are poor prognostic factors, were found to be significantly more common in high SUV_{max} values (≥14.65). The 5-year disease-free survival was 92.0% at low SUV_{max} and 71.1% in patients with high SUV_{max} values (p=0.004). Patients with low SUV_{max} had a higher mean 5-year overall survival than patients with high SUV_{max} (97.3% & 71.8%; p<0.001).

Conclusion: In order to predict the presence of LVSI in the preoperative period, the SUV_{max} value of the uterine lesion on PET-CT can be used. It may be helpful in planning the extent of the surgery and the level of LN dissection.

Keywords: Endometrial cancer, lymph node, lymphovascular space involvement, positron emission tomography.

Cite this article as: Gülseren V, Dolanbay M, Dağgez M, Abdülrezzak Ü, Çağlı F, Tutuş A, et al. Prediction of prognostic factors in endometrial cancer with PET-CT imaging. Zeynep Kamil Med J 2024;55(3):128–133.

Received: August 07, 2023 **Revised:** December 22, 2023 **Accepted:** March 22, 2024 **Online:** August 21, 2024
Correspondence: Varol GÜLSEREN, MD. Erciyes Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum Anabilim Dalı, Jinekolojik Onkoloji Kliniği, Kayseri, Türkiye.
Tel: +90 352 207 66 66 **e-mail:** drvarolgulseren@gmail.com

INTRODUCTION

The most common gynecological cancer type in developed countries is endometrial cancer (EC).[1] Histological type, grade, depth of myometrial invasion, lymph node (LN) metastasis and lymphovascular space involvement (LVSI) are important prognostic factors for recurrence and survival.[2] EC is usually diagnosed at an early stage (75%) and has an excellent prognosis.[3]

LVSI is the first step in tumor metastasis and is defined as the invasion of tumor cells in lymphatic and/or blood vessels. The presence of LVSI is associated with metastatic spread to lymph nodes and distant sites.[4] LVSI status is assessed by examining the hysterectomy material.[5] On the other hand, LVSI can rarely be evaluated in biopsy specimens, with the hazard of a second surgery to confirm lymph node metastasis.[6,7] Recently, the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) ESGO-ESTRO-ESP classification, based on final pathology taking into account both LVSI and lymph node status, identified four risk groups for recurrence and is used in adjuvant therapy.[7] Some authors have reported that pelvic and para-aortic lymphadenectomy in low-risk EC patients has no clinical benefit but causes an additional increase in the risk of complications and morbidities.[8] Although there were imaging studies evaluating LVSI preoperatively, no consensus was reached.[9] In addition, LVSI is now included in the 2023 EC staging system.[10]

The aim of our study is to evaluate the LVSI status using preoperative fluorine-18 (18F) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) imaging.

MATERIAL AND METHODS

This retrospective study was based on a review of the records of patients who were diagnosed with EC and underwent hysterectomy at the Gynecologic Oncology Clinic of Erciyes University, Faculty of Medicine, Türkiye, between January 2014 and 2021. The patients' clinical files and pathological specimens were reviewed retrospectively. Study inclusion was limited to patients with EC who were operated on at our institution, for whom follow-up data were available, and who underwent PET-CT in the preoperative period. Collected data included patient age at diagnosis, tumor size, histological subtype, lymphovascular space invasion, The International Federation of Gynecology and Obstetrics (FIGO) stage, and comorbidities (hypertension, diabetes mellitus). The study was approved by the local Ethics Committee (Date=26.05.2021, Decision No=2021/365) and conducted in accordance with the principles of the Declaration of Helsinki.

All surgical operations were carried out by surgeons experienced in gynecological oncologic surgery. A vertical midline incision was preferred in all patients for ease of access during abdominal exploration and organ resection. After the peritoneal cavity had been entered, a peritoneal wash was obtained for cytology. Exploration of the abdominal cavity included systematic examination of the peritoneal surfaces, omentum, colon and small intestine, and para-colic, pelvic, mesenteric, and para-aortic sites, as well as palpation to locate suspicious lesions. The procedures included hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, resection of bulky lymph nodes, and omentectomy. Systematic retroperitoneal lymphadenectomy was performed at our oncology center in patients with (a) myometrial invasion ≥1/2, (b) positive pelvic LNs, (c) nonendometrioid tumors, and (d) grade 3 endometrioid cancer. The staging of all cases was re-evaluated according to the FIGO 2023 staging system by re-evaluating the pathological findings.[10] Pelvic lymphadenectomy consisted of removal of the lymphatic tissue over the external, internal, and common iliac vessels and in the obturator fossa. Para-aortic LN dissection was performed by removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the bifurcation and proceeding to the left renal vein if necessary.

Table 1: The demographic and clinical characteristics of the patient (n=151)

Characteristics	
Age, years, Mean±SD	59.7±10.8
CA125, Mean±SD	58.5±143.2
Hemoglobin, Mean±SD	12.1±2.0
Histological grade, n (%)	
1	81 (53.6)
2	45 (29.8)
3	25 (16.6)
Myometrial invasion, n (%)	
Limited in the cavity	10 (6.6)
<1/2	104 (68.9)
≥1/2	34 (22.5)
Serosal	3 (2.0)
Cervical invasion, n (%)	17 (11.3)
Adnexal involvement, n (%)	5 (3.3)
Lymphovascular space invasion, n (%)	35 (23.2)
Stage, n (%)	
IA1	10 (6.6)
IA2	79 (52.3)
IA3	1 (0.7)
IB	10 (6.6)
IIA	1 (0.7)
IIB	12 (7.9)
IIC	16 (10.6)
IIIC1	8 (5.3)
IIIC2	6 (4.0)
IVB	8 (5.3)
SUV_{max} (uterine lesion), Mean±SD	14.2±9.2
Vertical size of the tumor in PET, mm, Mean±SD	39.3±20.7
Horizontal size of the tumor in PET, mm, Mean±SD	29.2±16.9
The largest tumor size in pathology, cm, Mean±SD	3.6±2.0

SD: Standard deviation.

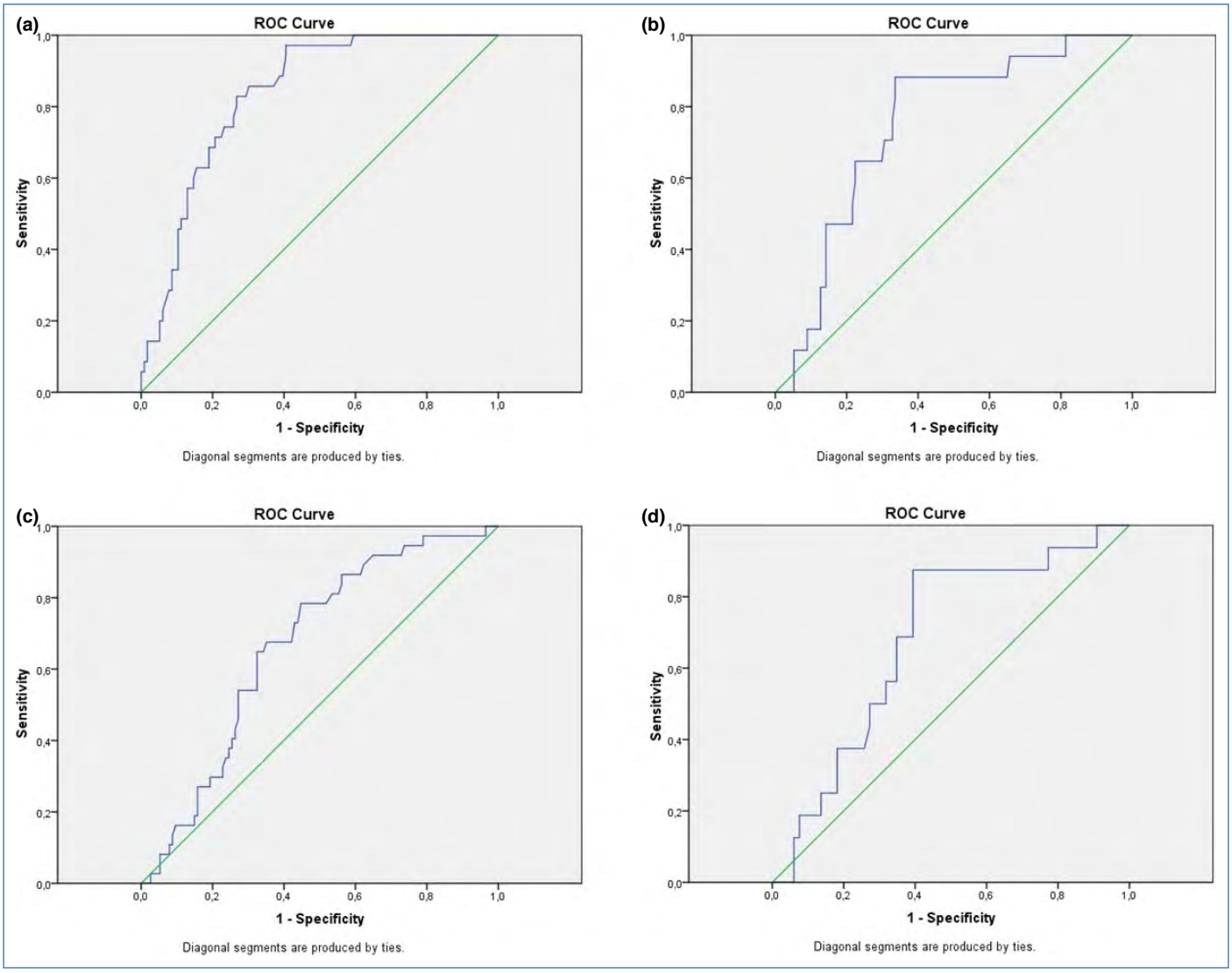

Figure 1: Determination of ideal cut-off values in PET-CT by ROC analysis to predict prognostic factors.

(a) LVSI & SUV_{max}, AUC: 0.834 (CI 95%: 0.769–0.899), p<0.001, cut-off: 14.6; sensitivity: 82.9% and 73.3% specificity. **(b)** Cervical involvement & SUV_{max}, AUC: 0.747 (CI 95%: 0.639–0.855), p=0.001, cut-off: 14.6; sensitivity: 88.2% and 66.4% specificity. **(c)** Deep myometrial invasion & SUV_{max}, AUC: 0.668 (CI 95%: 0.576–0.760), p=0.002, cut-off: 14.6; sensitivity: 64.9% and 67.5% specificity. **(d)** Lymph node metastasis & SUV_{max}, AUC: 0.680 (CI 95%: 0.544–0.817), p=0.026, cut-off: 14.6; sensitivity: 87.5% and 60.6% specificity.

All histological slides were reviewed by an expert gynecopathologist. Histological subtype, histological FIGO grade (according to the World Health Organization criteria), and mitotic index (number of mitoses per 10 high power fields) were evaluated both in the primary tumor and in curettage material. Uterine sections were selected from the anterior and posterior aspects of the cervix, the lower uterine segment, and the uterine corpus. A minimum of 6 sections, including the section showing the deepest tumoral invasion, was obtained for all specimens.

Diagnosis was confirmed histopathologically in all patients. The thickness and volume of the uterine lesion and its standardized uptake value (SUV_{max}) as obtained using 18F-FDG PET/CT and hysterectomy pathology results were recorded. Whole-body 18F-FDG PET/CT imaging was performed using a PET/CT scanner (Philips GeminiTF; Philips Healthcare, Andover, MA, USA), which consisted of a dedicated lutetium orthosilicate full-ring PET scanner and 16-slice CT. Both PET and low-dose CT scanning covered the skull to the proximal thigh. The protocol included 6 h of fasting before image acquisition, and all patients were asked to void before undergoing scanning. On the day of the examination, the serum glucose levels measured before 18F-FDG injections were found to be less than 140 mg/dL. Subsequently, 18F-FDG (6.5–13.4 µCi) was given intravenously 60 to 120 min before the CT scan, and the patients were instructed to rest in a semi-dark, temperate room between the injection and scanning. At 60 min after the administration of 18F-FDG, low-dose CT (50 mAs, 120 kV) covering the area from the skull to the proximal thighs was performed to attenuate the correction and precise anatomic localization. An emission scan was then conducted in the three-dimensional mode. All images were reconstructed and stored as axial, coronal, and sagittal slices. The total scanning time was about 20 min per patient. The SUV_{max} was estimated for each hypermetabolic lesion.

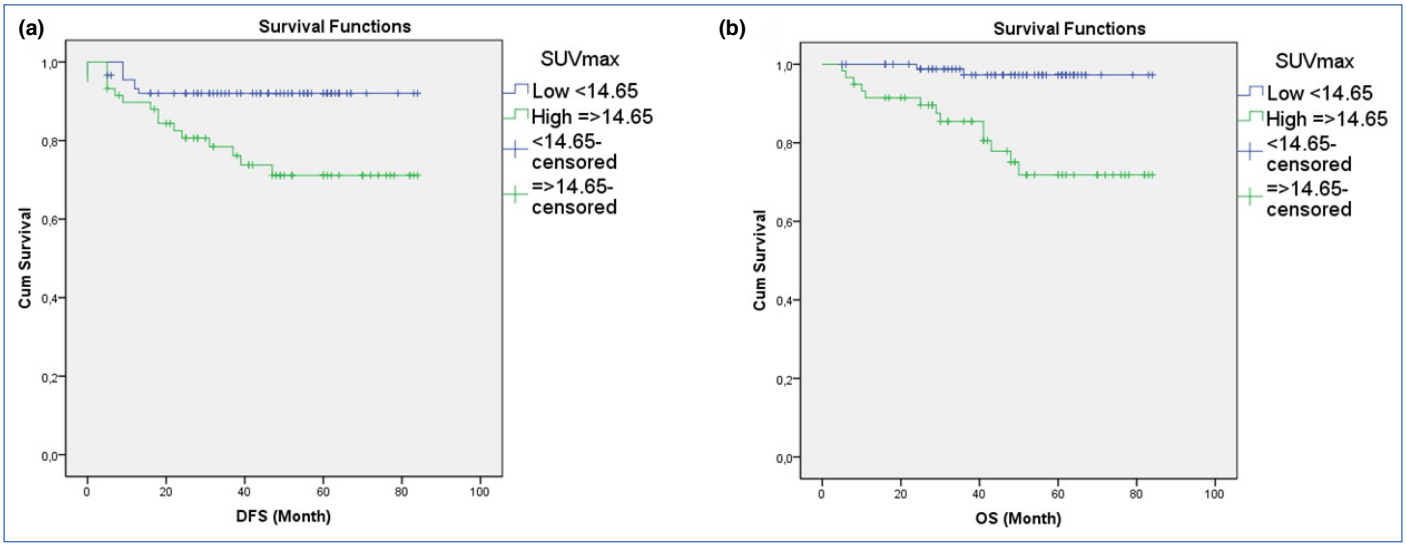

Figure 2: Disease-free **(a)** and overall **(b)** survival curves of low and high SUV_{max} values according to Kaplan-Meier.

The patients were followed up every 3–4 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. Disease-free survival was defined as the interval from the date of primary surgery to the detection of recurrence or the latest observation. Overall survival was defined as the interval from the date of primary surgery to death or the latest observation.

Statistical Analysis

Descriptive data are expressed as the mean±standard deviation or as a percentage. Chi-square was used to compare categorical data, and the Student t-test was used to compare nominal data. The optimal cut-off value of predictive prognostic factors in EC was identified using receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was used to define the risk factors for lymph node involvement; the results were presented as the 95% confidence interval (CI) and odds ratio (OR). All statistical analyses were performed using SPSS software (ver. 20.0; IBM Corp., Armonk, NY, USA). A p value <0.05 was considered to indicate statistical significance.

RESULTS

All 151 patients included in the study were of the endometrioid adenocarcinoma histological type. One hundred forty-one (93.4%) patients were estrogen receptor positive and 134 (88.7%) patients were progesterone receptor positive. Type 1 hysterectomy was performed in 148 (98.0%) patients and type 3 hysterectomy in 3 (2.0%) patients. Pelvic LN dissection was performed in 110 (72.8%) patients and paraaortic LN dissection was performed in 83 (55.0%) patients. The mean number of pelvic LNs taken was 17.1±7.9 and the number of paraaortic LNs was 6.1±4.2. Pelvic LN metastasis was observed in 16 (10.6%) patients and paraaortic LN metastasis was observed in 9 (6.0%) patients. Seventy-four (49.0%) of the patients had hypertension and 49 (32.5%) had diabetes mellitus. The demographic and clinical characteristics of the patients are given in Table 1.

Sixty-eight (45.0%) patients received adjuvant radiotherapy; vaginal brachytherapy (VBT) was given to 57 (37.7%) patients and external beam radiotherapy (EBRT) to 31 (21.5%) patients. Adjuvant chemotherapy was given to 21 (13.9%) patients and all received carboplatin plus paclitaxel. Recurrence was observed in 22 (14.6%) patients. Recurrence locations were: vaginal cuff in 3 (2.0%) patients, pelvic in 4 (2.6%) patients, pulmonary in 3 (2.0%) patients, common in more than one area in 8 (5.3%) patients, and other regions in 4 (2.6%) patients.

In order to predict LVSI, deep myometrial invasion, cervical involvement, and LN metastasis, ideal SUV_{max} values in preoperative PET-CT were analyzed according to ROC analysis in Figure 1. The sensitivity, specificity, negative and positive predictive values of the cut-off values are given in Table 2. The average incidence of prognostic factors with respect to low and high SUV_{max} values are summarized in Table 3. The 5-year disease-free survival (148 patients) was 92.0% at low SUV_{max} (<14.65) and 71.1% in patients with high SUV_{max} (≥14.65) values (p=0.004) (Fig. 2a). Patients with low SUV_{max} (<14.65) had a higher mean 5-year overall survival (141 patients) than patients with high SUV_{max} (≥14.65) (97.3% & 71.8%; p<0.001) (Fig. 2b).

DISCUSSION

In EC, depending on the status of prognostic factors, the extent of surgery and adjuvant treatment is decided. However, it may not always be possible to identify prognostic factors preoperatively. LVSI is defined as the presence of adenocarcinoma, of any extent, in endothelial-lined channels of uterine specimens extracted at the time of surgery.[11] In particular, the status of LVSI is not considered reliable if it is negative in preoperative biopsies because the absence of LVSI in the biopsy area does not reflect the LVSI status in the rest of the specimen. In this regard, we conducted research to predict the LVSI status and other prognostic features of EC patients according to SUV_{max} values in PET-CT, with an aim to guide the surgery.

LVSI is an important prognostic factor for disease relapse and poor survival in EC, as is LN metastasis, in patients with EC.[12–14] LVSI is reported as positive in 13.2–51.8% of ECs.[4,12–15] There are

Table 2: The sensitivity, specificity, negative and positive predictive value of the cut-off values

	Sensitivite	Spesifisite	PPV	NPV
Deep myometrial invasion	64.9	67.5	38.3	84.6
Cervical invasion	88.2	66.4	25.0	97.8
Lymphovascular space invasion	82.9	73.3	48.3	93.4
Lymph node involvement	87.5	60.6	35.0	95.2

PPV: Positive predictive value; NPV: Negative predictive value.

Table 3: Incidence of prognostic factors according to low and high SUV_{max} values

	Low SUV_{max} (<14.65) (n=91)	High SUV_{max} (≥14.65) (n=60)	p
Deep myometrial invasion	14 (15.4%)	23 (38.3%)	0.002
Cervical invasion	2 (2.2%)	15 (25.0%)	<0.001
Lymphovascular space invasion	6 (6.6%)	29 (48.3%)	<0.001
Lymph node involvement	2 (4.8%)	14 (35.0)	0.001

SUV: Standardized uptake value.

studies in the literature evaluating the utilization of PET-CT in LVSI assessment. SUV_{max} value of the uterine lesion was found to be significantly higher in patients with positive LVSI.[13–18] However, studies investigating the ideal cut-off value to detect LVSI positivity have reported a wide range of SUV_{max} values changing between 6–16.[16,17] Sensitivity of SUV_{max} for determining LVSI was 71.4–88.2%.[16–18] In regression analysis, the SUV_{max} value was significantly correlated with LVSI.[19] Apart from that, the relationship between deep myometrial invasion, advanced stage, LN involvement, and SUV_{max} values was investigated and a significant result was found.[14,19] The rate of LVSI positivity in patients with EC was 23.2% in our study. In regard to determining the LVSI status, the cut-off value of SUV_{max} was 14.6 in the ROC analysis, and the area under the curve was 0.834. The sensitivity was 82.9%, the negative predictive value was 93.4%, and the positive predictive value was 48.3%. Additionally, for disease-free and overall survival outcomes, patients with higher SUV_{max} values were found to be statistically significantly worse.

The choice of optimal surgery for EC, particularly on the extension of lymphadenectomy, should be balanced in terms of surgical morbidity and oncological outcomes. Surgeons may stand in favor of more comprehensive surgery to overcome endometrial cancer with high-risk factors. On the other hand, it is known that more radical surgery is associated with increased morbidity. It is known that systematic total pelvic and paraaortic lymphadenectomy increases complication rates such as wound infection, lymphocyst, and lymphedema. Preoperative evaluation and imaging may help in planning the extent of surgery. In our cohort, 6.6% of patients with low SUV_{max} values had LVSI positivity, while approximately half of the patients with high values were LVSI positive. When performing LN dissection, a more systematic approach should be performed in cases where the SUV_{max} values are above the threshold. In the ESGO-ESTRO-ESP guidelines on EC, LVSI is accepted as an important risk factor for disease recurrence and having information on the status of LVSI preoperatively may provide clarity in management.[7,9,11] In addition, LVSI changes the stage in the 2023 FIGO staging system.[10]

This study has some limitations. First, it has a retrospective design, and secondly, the sample size was relatively small. Further studies with larger cohorts and prospective designs are recommended. Lastly, systematic LN dissection was not performed for all patients. Despite these limitations, the comparable demographic characteristics of the study population and the inclusion of expert pathologists increased the validity of our results and reduced these weaknesses.

CONCLUSION

In conclusion, in order to predict the presence of LVSI in the preoperative period, the SUV_{max} value of the uterine lesion on PET-CT can be used. It may be helpful preoperatively in determining prognosis.

Statement

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 26.05.2021, number: 2021/365).

Author Contributions: Concept – MD; Design – ÜA, FÇ; Supervision – SS, BÖ; Data Collection and/or Processing – MDa; Analysis and/or Interpretation – VG; Literature Search – AT; Writing – VG; Critical Reviews – KG.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
2. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet 2016;387:1094–108.
3. Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. J Epidemiol Biostat 2001;6:47–86.
4. Boothe D, Wolfson A, Christensen M, Francis S, Werner TL, Gaffney DK. Lymphovascular invasion in endometrial cancer: Prognostic value and implications on adjuvant radiation therapy use. Am J Clin Oncol 2019;42:549–54.
5. Sadozye AH, Harrand RL, Reed NS. Lymphovascular space invasion as a risk factor in early endometrial cancer. Curr Oncol Rep 2016;18:24.
6. Ueno Y, Forghani B, Forghani R, Dohan A, Zeng XZ, Chamming's F, et al. Endometrial carcinoma: MR imaging-based texture model for preoperative risk stratification-a preliminary analysis. Radiology 2017;284:748–57.
7. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021;31:12–39.
8. Hidaka T, Kato K, Yonezawa R, Shima T, Nakashima A, Nagira K, et al. Omission of lymphadenectomy is possible for low-risk corpus cancer. Eur J Surg Oncol 2007;33:86–90.
9. Nougaret S, Reinhold C, Alsharif SS, Addley H, Arceneau J, Molinari N, et al. Endometrial cancer: Combined MR volumetry and diffusion-weighted imaging for assessment of myometrial and lymphovascular invasion and tumor grade. Radiology 2015;276:797–808.
10. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet 2023;162:383–94.
11. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–51.
12. Mapelli P, Ironi G, Bergamini A, Mangili G, Rancoita PM, Taccagni GL, et al. Synergic role of preoperative 18F-fluorodeoxyglucose PET and MRI parameters in predicting histopathological features of endometrial cancer. Nucl Med Commun 2020;41:1073–80.
13. Kitajima K, Suenaga Y, Ueno Y, Maeda T, Ebina Y, Yamada H, et al. Preoperative risk stratification using metabolic parameters of (18)F-FDG PET/CT in patients with endometrial cancer. Eur J Nucl Med Mol Imaging 2015;42:1268–75.
14. Sürer Budak E, Toptaş T, Aydın F, Öner AO, Çevikol C, Şimşek T. Correlation of minimum apparent diffusion coefficient and maximum standardized uptake value of the primary tumor with clinicopathologic characteristics in endometrial cancer. Mol Imaging Radionucl Ther 2017;26:24–32.
15. Sahin H, Sarioglu FC, Bagci M, Karadeniz T, Uluer H, Sanci M. Preoperative magnetic resonance volumetry in predicting myometrial invasion, lymphovascular space invasion, and tumor grade: Is it valuable in international federation of gynecology and obstetrics stage I endometrial cancer? Int J Gynecol Cancer 2018;28:666–74.
16. Yahata T, Yagi S, Mabuchi Y, Tanizaki Y, Kobayashi A, Yamamoto M, et al. Prognostic impact of primary tumor SUVmax on preoperative 18F-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography in endometrial cancer and uterine carcinosarcoma. Mol Clin Oncol 2016;5:467–74.
17. Sudo S, Hattori N, Manabe O, Kato F, Mimura R, Magota K, et al. FDG PET/CT diagnostic criteria may need adjustment based on MRI to estimate the presurgical risk of extrapelvic infiltration in patients with uterine endometrial cancer. Eur J Nucl Med Mol Imaging 2015;42:676–84.
18. Liu DD, Li J, Li X, Xie L, Qin L, Peng F, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis from ^{18}F-FDG PET/CT in lymph node metastases and risk stratification of endometrial carcinoma. J Gynecol Oncol 2019;30:e89.
19. Lee HJ, Ahn BC, Hong CM, Song BI, Kim HW, Kang S, et al. Preoperative risk stratification using (18)F-FDG PET/CT in women with endometrial cancer. Nuklearmedizin 2011;50:204–13.