Is the measurement of the size of uterine lesions with positron emission tomography consistent in pre- and postmenopausal periods in endometrioid-type endometrial cancer?

Endometrioid tip endometriyal kanserde, pre- ve postmenopozal dönemlerde pozitron emisyon tomografisi ile uterin lezyon boyutunun ölçümleri tutarlı mıdır?

Varol Gülseren1, Mustafa Kocaer2, Özgü Çelikkol Güngördük3, Isa Aykut Özdemir4, Muzaffer Sancı2, Kemal Güngördük3

1Kaman State Hospital, Clinic of Obstetrics and Gynecology, Kırşehir, Turkey
2University of Health Sciences, Clinic of Gynecologic Oncology, İzmir, Turkey
3Muğla Sıtkı Koçman University, Training and Research Hospital, Department of Gynecology and Oncology, Muğla, Turkey
4Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Gynecology and Oncology, İstanbul, Turkey

Abstract

Objective: We aimed to investigate the correlation of the size and volume of uterine tumors obtained using positron emission tomography/computed tomography (PET/CT) and pathology specimens in patients with endometrioid-type endometrial cancer (EEC) in the premenopausal period, and to compare the results with those of postmenopausal women. In the premenopausal period, the endometrium uses more glucose than in the postmenopausal period. Therefore, the measurement of uterine tumor size using PET/CT in the premenopausal period may normally be different.

Materials and Methods: In this retrospective study, we reviewed the records of patients who were diagnosed as having EEC and underwent hysterectomy. Only patients who underwent preoperative PET/CT imaging were included in the study. The thickness and volume of the uterine lesion, and its maximum standardized uptake value as obtained using PET/CT and hysterectomy pathology specimens were recorded.

Results: Tumor size (p=0.051) and volume (p=0.404) were not found to be correlated with the imaging method used in premenopausal women and pathologic specimens. However, there was a correlation in postmenopausal women (p<0.001 for tumor size and p<0.001 for tumor volume). PET/CT has higher sensitivity, specificity, and positive predictive value in the postmenopausal period in the detection of >20 mm uterine tumors.

Conclusion: PET/CT has a limited role in the measurement of the size of uterine lesions in all patients, especially in the premenopausal period; therefore, we recommend that frozen-section examinations be used intraoperatively to decide on lymph node dissection.

Keywords: Positron emission tomography/computed tomography, endometrial cancer, premenopausal and reproductive periods

Öz

Amaç: Endometrioid tip endometriyal kanser (EEK) olan hastalarda pozitron emisyon tomografisi/bilgisayarlı tomografi (PET/CT) ve patoloji örnekleri ile elde edilen uterin tümörlerin boyut ve hacimlerinin korelasyonunu ve premenopozal dönem ile postmenopozal dönemları karşılaştırmayı amaçladık. Premenopozal dönemde, endometrium, postmenopozal dönemde kıyasla daha fazla glukoz kullanır. Bu nedenle, premenopozal dönemde uterin tümör büyüklüğünün normalden farklı olabilir.

Gereç ve Yöntemler: Bu retrospektif çalışmada, EEE tanısı alan ve histerektomi yapılan hastaların kayıtları gözden geçirildi. Sadece preoperatif PET/CT görüntüleme yapılan hastalar çalışmaya dahil edildi. Uterin lezyonun kalınlığı, hacmi ve maksimum standardize alınan değerleri PET/CT ve histerektomi ile patoloji örnekleri tarafından elde edilen veriler kaydedildi.

Bulgulan: Premenopozal çağdaaki kadınlarda tümör boyutu (p=0.051) ve hacmi (p=0.404) görüntülene yöntemi ve patolojik örnekler arasında korelasyon bulunmadı. Bununla birlikte, postmenopozal kadınlarda bir korelasyon vardır (p<0.001 tümör boyutu için ve p<0.001 tümör hacmi için). PET/CT, >20 mm uterin tümörü tanınamada postmenopozal dönemde daha yüksek sensitivite, spesifite ve pozitif prediktif değere sahipti.
Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries\(^1\)\(^-\)\(^3\). Prognosis is affected by the age of the patient, histologic type and grade of the tumor, cervical invasion, depth of myometrial invasion, lymph node involvement, and distant organ metastasis\(^1\)\(^-\)\(^2\). Fluorine-18 (\(^{18}\)F) fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is an imaging modality used to obtain anatomic and metabolic data on cancer cells in numerous malignancies\(^2\)\(^-\)\(^3\). It is helpful to evaluate tumor perfusion and metabolism screening using the following radioisotopes: carbon-11, \(^{18}\)F, nitrogen-13, oxygen-15 and rubidium-82\(^4\)^\(^-\)\(^6\). Of these, \(^{18}\)F-FDG passes through the cell membrane in the same way as glucose and is effectively trapped when it is phosphorylated and cannot be metabolized by the following enzyme: phosphofructokinase-1. Thus, \(^{18}\)F-FDG remaining within the cell reflects glucose uptake into the cell\(^6\). The standardized uptake value (SUV) is accepted as an indicator of tumor aggressiveness and a marker for metabolic alterations in cancer tissues\(^2\)\(^-\)\(^4\). The maximum SUV (SUV\(_{\text{max}}\)) has been associated with the tumor proliferation rate, tumor grade, and expression of glucose transporters\(^2\)\(^-\)\(^4\). About 25% of patients with endometrioid-type endometrial cancer (EEC) are in the premenopausal periods\(^5\). In women of the premenopausal period, physiologic FDG accumulation in the uterus should be considered when focal FDG accumulation is observed in the pelvis\(^5\). In the endometrium, normal uptake of \(^{18}\)F-FDG PET/CT in patients who are premenopausal varies cyclically and increases in the ovulatory and menstrual phases\(^7\). In the premenopausal period, the endometrium consumes constant energy for proliferation and the secretory phases\(^8\). In the present study, we aimed to investigate the correlation of the size and volume of uterine tumors obtained using PET/CT and pathology specimens in patients with EEC in the premenopausal period and to compare the results with those of postmenopausal women.

Materials and Methods

In this retrospective study, we reviewed the records of patients who were diagnosed as having EEC and underwent hysterectomy at the Tepecik Training and Research Hospital, Clinic of Gynecologic Oncology between January 2012 and August 2016. Only patients who underwent preoperative \(^{18}\)F-FDG PET/CT imaging were included in the study. A flowchart of the study is shown in Figure 1. Diagnosis was confirmed histopathologically in all patients. The thickness and volume of the uterine lesion and its SUV\(_{\text{max}}\) value as obtained using \(^{18}\)F-FDG PET/CT and hysterectomy pathology specimens were recorded. Data including age, menopausal status, and comorbidities were recorded. Tumor staging was performed based on the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging criteria\(^8\). The study was approved by the local ethics committee (Katip Celebi University, approval number: 45, Date: 27/02/2014). Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki. All surgical specimens were evaluated by specialized gynecologic pathologists. The inclusion criteria were as follows: 1) all types of histology, 2) no intraoperative evidence of extrauterine spread, 3) performance of pelvic and paraortic lymphadenectomy, and 4) histopathologically proven cervical stromal involvement. Uterine sections were selected from anterior and posterior aspects of the cervix, lower uterine segment, and uterine corpus. A minimum of 6 sections including a section of the deepest tumoral invasion was obtained for all specimens. Whole-body \(^{18}\)F-FDG PET/CT images were performed using a PET/CT scanner (Philips Gemini TF; 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 \(^{18}\)F-FDG injections were found to be less than 140 mg/dL. Subsequently, \(^{18}\)F-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 \(^{18}\)F-FDG, low-dose CT (50 mAs, 120 kV) covering the area from scull 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$_{\text{max}}$ was estimated for each hypermetabolic lesion.

**Statistical Analysis**

This study was calculated to have 94% power and 71% effect size using the G power analysis program (Faul, Erdfelder, Lang and Buchner, 2007; version 3.0). Statistical analysis was performed using the Med-Calc for Windows version 16.0 statistical software (MedCalc Software, Mariakerke, Belgium). Descriptive data are expressed in mean ± standard deviation and percentages. Student’s t-test was used to compare the mean values between two independent groups, and the chi-square ($\chi^2$) test was used to compare nominal values between the two groups. Correlation analysis was performed using bivariate correlation analysis. The sensitivity, specificity, negative and positive predictive values of the $^{18}$F-FDG PET/CT were also calculated. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of predictive tumor size $>2$ cm in uterus lesion with EEC. A $p$ value of $<0.05$ was considered statistically significant.

**Results**

Of all patients with EEC who underwent $^{18}$F-FDG PET/CT, 38 women were premenopausal, and 112 were postmenopausal. The demographic and clinical characteristics of the patients are shown in Table 1.

The largest tumor size and total volume of both premenopausal and postmenopausal patients in the $^{18}$F-FDG PET/CT reports were compared with the pathology reports. The correlation analysis results are shown in Figures 2 and 3. The tumor size and volume were not found to be correlated with the imaging method used in premenopausal women and pathologic specimens for tumor size and tumor volume ($p=0.051$, correlation coefficient: 0.319; $p=0.404$, correlation coefficient: 0.139, respectively). However, there was a correlation in postmenopausal women for tumor size and tumor volume ($p<0.001$, correlation coefficient: 0.772; $p<0.001$ and correlation coefficient: 0.695, respectively). Sensitivity and specificity tests were performed in the premenopausal women and postmenopausal women by dividing the tumor size into the two groups ($\leq 20$ mm; $>20$ mm) in both $^{18}$F-FDG PET/CT reports and pathology specimens. In the former group, the sensitivity of $^{18}$F-FDG PET/CT to detect $>20$ mm tumors was 19/21 (90.4%), specificity was 6/17 (35.2%), the negative predictive value was 6/8 (75.0%), and

**Table 1. Demographic characteristics and clinical characteristics of the patients**

|                      | Premenopausal (n=38) | Postmenopausal (n=112) | p    |
|----------------------|----------------------|------------------------|------|
| Age, mean ± SD       | 44.1±4.8             | 62.6±7.5               | <0.001|
| Gravida, mean ± SD   | 2.4±1.9              | 3.3±2.2                | 0.082 |
| Parity, mean ± SD    | 1.9±1.6              | 2.8±1.9                | 0.046 |
| BMI, mean ± SD       | 30.1±5.1             | 33.1±5.7               | 0.093 |
| CA125, mean ± SD     | 136.7±264.4          | 219.9±570.0            | 0.394 |
| Hematocrit, mean ± SD| 38.0±4.3             | 38.8±3.6               | 0.234 |
| Hypertension, n (%)  | 6 (15.7)             | 45 (40.1)              | <0.001|
| Diabetes, n (%)      | 4 (10.5)             | 31 (27.6)              | 0.005 |
| Histologic grade, n (%) |                   |                        | 0.774 |
| I                    | 15 (39.4)            | 38 (33.9)              |      |
| II                   | 18 (47.3)            | 62 (55.3)              |      |
| III                  | 5 (13.1)             | 12 (10.7)              |      |
| LVSI, n (%) positive | 13 (34.2)            | 44 (39.2)              | 0.633 |
| SUV$_{\text{max}},$ mean ± SD | 13.4±5.9           | 15.7±6.5               | 0.062 |

BMI: Body mass index, CA125: Cancer antigen 125, LVSI: Lymphovascular space invasion, SUV$_{\text{max}}$: The maximum standardized uptake value, SD: Standard deviation

**Figure 2. Correlation analysis* between $^{18}$F-FDG PET/CT and pathology report of tumor size**

$^{18}$F-FDG PET/CT: $^{18}$-Florin-Fluorodeoxyglucose-positron emission tomography/computed tomography, *: Spearman’s correlation analysis, $p=0.051$ for premenopausal, $p=0.001$ for postmenopausal

**Figure 3. Correlation analysis* between $^{18}$F-FDG PET/CT and pathology report of tumor volume**

$^{18}$F-FDG PET/CT: $^{18}$ Florin-Fluorodeoxyglucose positron emission tomography/computed tomography, *: Spearman’s correlation analysis, $p=0.404$ for premenopausal, $p<0.001$ for postmenopausal
In this retrospective study, we evaluated the accuracy of 18F-FDG PET/CT to detect >20 mm tumors was 93.6%, specificity was 61.1%, and the negative and positive predictive values were 64.7% and 92.6%, respectively. The proposed cut-offs for SUV\textsubscript{max} for these parameters to identify deep myometrial invasion in the literature is a relatively wide range, 9-18\textsuperscript{(8,10)}. There was a significant association reported between the SUV\textsubscript{max} of the primary tumors and maximum tumor size (p=0.001), but not between the SUV\textsubscript{max} and menopause state (p=0.522)\textsuperscript{(11)}. In our cohort, SUV\textsubscript{max} >10.5 had 82.1% sensitivity and 73.5% specificity for tumors >2 cm. The 18F-FDG PET/CT imaging modality uses the intracellular glucose metabolism of tumor cells\textsuperscript{(6)}. In the premenopausal period, the endometrium uses different amounts of glucose for menstruation, proliferation, ovulation, and secretion processes; however, the endometrium in the postmenopausal period uses less glucose\textsuperscript{(6)}. In a study of endometrial 18F-FDG uptake in gynecologic malignancies in premenopausal women by Lerman et al.,\textsuperscript{(7)} the mean SUV values were 5.0±3.2 in the menstrual phase, 2.6±1.1 in the proliferation phase, 3.7±0.9 in the ovulation phase, and 2.5±1.1 in the secretory phase (p<0.001). In the aforementioned study, the mean SUV value of the patients with abnormal cycles was 3.4±1.4 in patients with oligomenorrhea and 1.9±1.2 in patients with amenorrhea (p=0.02). PET may be influenced by tissue type\textsuperscript{(9)}. The efficacy of PET/CT may be affected by the size of the tumor, and thus PET/CT may be limited for the detection of small tumors\textsuperscript{(9)}. Furthermore, oral contraceptive use has been shown to affect the 18F-FDG uptake in the endometrium\textsuperscript{(12)}. In our study, we hypothesized that 18F-FDG uptake in premenopausal women and the calculated tumor size and volume would be less correlated with the pathology specimens compared with postmenopausal women. In our study population, the calculated tumor size (p=0.051) and volume (p=0.404) on 18F-FDG PET/CT imaging in premenopausal women were not correlated with the pathology specimens. However, in the postmenopausal period, tumor size (p<0.001) and volume (p<0.001) on the 18F-FDG PET/CT scan were found to correlate with the pathology specimens. In addition, the sensitivity and specificity of the PET/CT to detect lymph node metastasis in premenopausal women was 80.0% and 84.8%, respectively, compared with 80.0% and 93.8% in postmenopausal women, respectively. The sensitivity was 40.9% in micrometastatic lymph nodes with (metastasis >2 mm) and 52.9% in those with (metastasis >5 mm)\textsuperscript{(9)}. The sensitivity and specificity values for detecting lymph node involvement are similar in pre- and postmenopausal women, estimating the size of primary uterine lesions showed limited correlation in premenopausal women. In our cohort, there was no statistically significant difference between the SUV\textsubscript{max} values of pre- and postmenopausal period uterine lesions. Therefore, we consider that PET/CT has a limited role in deciding for lymph node dissection in premenopausal women, and frozen-section examinations should be performed during surgery. In

Figure 4. ROC curve associated with the maximum standardized uptake value to identify patients with tumor size >2 mm. The area under the curve was 0.791 (p<0.001) ROC curve: The maximum standardized uptake value

the positive predictive value was 19/30 (63.3%). The pooled diagnostic indices to detect tumors >20 mm in postmenopausal women were as follows: sensitivity 88/94 (93.6%), specificity 11/18 (61.1%), negative predictive value 11/17 (64.7%), and positive predictive value 88/95 (92.6%). The optimal SUV\textsubscript{max} value was investigated using ROC analysis to distinguish patients with tumor size >2 cm. The ROC analysis is shown in Figure 4 (p<0.001, area under the curve=0.791). SUV\textsubscript{max} values of 10.5 and above were found as 82.1% sensitivity and 73.5% specificity, 28/29 (96.6%) negative predictive value, and 28/33 (84.8%) specificity, 11/18 (61.1%), negative predictive value 11/17 (64.7%), and positive predictive value 88/95 (92.6%). The optimal SUV\textsubscript{max} value was investigated using ROC analysis to distinguish patients with tumor size >2 cm. The ROC analysis is shown in Figure 4 (p<0.001, area under the curve=0.791). SUV\textsubscript{max} values of 10.5 and above were found as 82.1% sensitivity and 73.5% specificity, 28/29 (96.6%) negative predictive value, and 28/33 (84.8%) specificity, 11/18 (61.1%), negative predictive value 11/17 (64.7%), and positive predictive value 88/95 (92.6%). The proposed cut-offs for SUV\textsubscript{max} for these parameters to identify deep myometrial invasion in the literature is a relatively wide range, 9-18\textsuperscript{(8,10)}. There was a significant association reported between the SUV\textsubscript{max} of the primary tumors and maximum tumor size (p=0.001), but not between the SUV\textsubscript{max} and menopause state (p=0.522)\textsuperscript{(11)}. In our cohort, SUV\textsubscript{max} >10.5 had 82.1% sensitivity and 73.5% specificity for tumors >2 cm. The 18F-FDG PET/CT imaging modality uses the intracellular glucose metabolism of tumor cells\textsuperscript{(6)}. In the premenopausal period, the endometrium uses different amounts of glucose for menstruation, proliferation, ovulation, and secretion processes; however, the endometrium in the postmenopausal period uses less glucose\textsuperscript{(6)}. In a study of endometrial 18F-FDG uptake in gynecologic malignancies in premenopausal women by Lerman et al.,\textsuperscript{(7)} the mean SUV values were 5.0±3.2 in the menstrual phase, 2.6±1.1 in the proliferation phase, 3.7±0.9 in the ovulation phase, and 2.5±1.1 in the secretory phase (p<0.001). In the aforementioned study, the mean SUV value of the patients with abnormal cycles was 3.4±1.4 in patients with oligomenorrhea and 1.9±1.2 in patients with amenorrhea (p=0.02). PET may be influenced by tissue type\textsuperscript{(9)}. The efficacy of PET/CT may be affected by the size of the tumor, and thus PET/CT may be limited for the detection of small tumors\textsuperscript{(9)}. Furthermore, oral contraceptive use has been shown to affect the 18F-FDG uptake in the endometrium\textsuperscript{(12)}. In our study, we hypothesized that 18F-FDG uptake in premenopausal women and the calculated tumor size and volume would be less correlated with the pathology specimens compared with postmenopausal women. In our study population, the calculated tumor size (p=0.051) and volume (p=0.404) on 18F-FDG PET/CT imaging in premenopausal women were not correlated with the pathology specimens. However, in the postmenopausal period, tumor size (p<0.001) and volume (p<0.001) on the 18F-FDG PET/CT scan were found to correlate with the pathology specimens. In addition, the sensitivity and specificity of the PET/CT to detect lymph node metastasis in premenopausal women was 80.0% and 84.8%, respectively, compared with 80.0% and 93.8% in postmenopausal women, respectively. The sensitivity was 40.9% in micrometastatic lymph nodes with (metastasis >2 mm) and 52.9% in those with (metastasis >5 mm)\textsuperscript{(9)}. The sensitivity and specificity values for detecting lymph node involvement are similar in pre- and postmenopausal women, estimating the size of primary uterine lesions showed limited correlation in premenopausal women. In our cohort, there was no statistically significant difference between the SUV\textsubscript{max} values of pre- and postmenopausal period uterine lesions. Therefore, we consider that PET/CT has a limited role in deciding for lymph node dissection in premenopausal women, and frozen-section examinations should be performed during surgery. In
our cohort, we found that there were statistically significantly more patients with diabetes among the postmenopausal patients (p=0.005). However, previous studies reported that PET/CT could be applied to diabetics. In all patients (diabetics and non-diabetics), the serum glucose levels measured before 18F-FDG injections were found to be less than 140 mg/dL.

Study Limitations

Nonetheless, there are some limitations to this study. First, the study has a retrospective design. Second, the sample size is relatively small. Third, the endometrial phases of premenopausal women are still missing aspects of the study. Despite these limitations, the similarities of the demographic characteristics in the study population and analysis reports of the expert pathologists and radiologists increased the validity of our results and diminished the weaknesses. However, further large-scale, prospective studies are required to shed light on the role of 18F-FDG PET/CT in EEC.

Conclusion

In conclusion, our study results suggest that 18F-FDG PET/CT has a limited role in the measurement of the size of the uterine lesion in all patients, especially in the premenopausal period; therefore, we recommend that frozen-section examinations should be performed intraoperatively to decide on lymph node dissection.

Ethics

Ethics Committee Approval: The study was approved by the Katip Çelebi University Local Ethics Committee (approval number: 45, Date: 27/02/2014).

Informed Consent: Consent form was filled out by all participants.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.A.Ö., M.S., Concept: V.G., K.G., Design: M.K., K.G., Data Collection or Processing: M.K., Ö.C.G., Analysis or Interpretation: V.G., Ö.C.G., Literature Search: V.G., İ.A.Ö., Writing: V.G., M.K.

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

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

References

1. Amani F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet 2005;366:491-505.
2. Ö zgü E, Öz M, Yıldız Y, Ö zgü BS, Erkaya S, Güngör T. Prognostic value of 18F-FDG PET/CT for identifying high- and low-risk endometrial cancer patients. Ginekol Pol 2016;87:493-7.
3. Nakamura K, Kodama J, Okumura Y, Hongo A, Kanazawa S, Hiramatsu Y. The SUVmax of 18F-FDG PET Correlates With Histological Grade in Endometrial Cancer. Int J Gynecol Cancer 2010;20:110-5.
4. Croteau E, Renaud JM, Richard MA, Ruddy TD, Benard F, de Kemp RA. PET Metabolic Biomarkers for Cancer. Biomark Cancer 2016;8(Suppl 2):61-9.
5. Boonya-ussadorn T, Choi WH, Hyun OJ, Kim SH, Chung SK, Yoo R. 18F-FDG PET/CT Findings in Endometrial Cancer Patients: The Correlation between SUVmax and Clinicopathologic Features. J Med Assoc Thai 2014;97:S115-22.
6. Chander S, Meltzer CC, McCook BM. Physiologic uterine uptake of FDG during menstruation demonstrated with serial combined positron emission tomography and computed tomography. Clin Nucl Med 2002;27:22-4.
7. Haldorsen IS, Salvesen HB. What is the Best Preoperative Imaging for Endometrial Cancer? Curr Oncol Rep 2016;18:25.
8. Lerman H, Metser U, Grisaru D, Fishman A, Lievshitz G, Even-Sapir E. Normal and Abnormal 18F-FDG Endometrial and Ovarian Uptake in Pre- and Postmenopausal Patients: Assessment by PET/CT. J Nucl Med 2004;45:266-71.
9. Haldorsen IS, Salvesen HB. What is the Best Preoperative Imaging for Endometrial Cancer? Curr Oncol Rep 2016;18:25.