
Normal and Abnormal ^{18}F -FDG Endometrial and Ovarian Uptake in Pre- and Postmenopausal Patients: Assessment by PET/CT

Hedva Lerman, MD¹; Ur Metser, MD¹; Dan Grisaru, MD, PhD^{2,3}; Ami Fishman, MD^{3,4}; Gennady Lievshitz, MD¹; and Einat Even-Sapir, MD, PhD^{1,3}

¹Department of Nuclear Medicine, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; ²Department of Gynecology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; ³Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; and ⁴Department of Obstetrics and Gynecology, Sapir Medical Center, Kfar Sava, Israel

The purpose of the study was to assess physiologic endometrial ^{18}F -FDG uptake during the 4 phases of the menstrual cycle and to differentiate between physiologic and malignant endometrial uptake. **Methods:** Endometrial ^{18}F -FDG uptake, expressed as standardized uptake value (SUV), was measured on PET/CT images of 285 consecutive female patients, of whom 246 (112 premenopausal and 134 postmenopausal) had no known gynecologic malignancy and 39 (14 premenopausal and 25 postmenopausal) had cervical, endometrial, or ovarian cancer. **Results:** Two peaks of increased endometrial ^{18}F -FDG uptake were identified during the 4-phase cycle. The mean SUVs were 5 ± 3.2 and 3.7 ± 0.9 in menstruating and ovulating patients, respectively, and 2.6 ± 1.1 and 2.5 ± 1.1 in patients in the proliferative and secretory phases, respectively. The mean endometrial SUV in postmenopausal patients not receiving hormonal therapy was 1.7 ± 0.5 . Oligomenorrhea and benign endometrial abnormalities were associated with increased ^{18}F -FDG uptake. Neither contraceptives nor hormonal therapy was associated with a significant increase in endometrial uptake. In addition to the increased tumor uptake measured in patients with cervical cancer (14.9 ± 7.3 in postmenopausal patients and 12.2 ± 6.6 in premenopausal patients), increased uptake was also found in the adjacent endometrium, although it appeared normal on CT (4.8 ± 2 in premenopausal patients and 4.7 ± 2.8 in postmenopausal patients). Increased ovarian ^{18}F -FDG uptake was detected in 7 patients with ovarian cancer (9.1 ± 4) and in 21 premenopausal patients without known ovarian malignancy (5.7 ± 1.5 , $P < 0.01$), of whom 15 were at mid cycle and 3 reported oligomenorrhea. An ovarian SUV of 7.9 separated benign from malignant uptake with a sensitivity of 57% and a specificity of 95%. **Conclusion:** In premenopausal patients, normal endometrial uptake of ^{18}F -FDG changes cyclically, increasing during the ovulatory and menstrual phases. Increased uptake in the endometrium adjacent to a cervical tumor does not necessarily reflect endometrial tumor invasion. Increased ovarian uptake in postmenopausal patients is associated with

malignancy, whereas increased ovarian uptake may be functional in premenopausal patients.

Key Words: ^{18}F -FDG; physiologic uptake; endometrium; cervical cancer; PET/CT

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Gynecologic malignancies, including cervical, endometrial, vulvar, and ovarian carcinoma, have been found to show ^{18}F -FDG avidity, and clinical application of ^{18}F -FDG PET in this patient population is emerging. Many studies on patients with cervical cancer have focused on noninvasive lymph node staging and detection of unsuspected distant metastases. ^{18}F -FDG PET has been found to be more accurate for the assessment of lymph node involvement than are morphologic modalities such as CT and MRI, which depend mostly on size criteria. Assessment of tumor volume with PET was found to be an independent prognostic factor and a better predictor of prognosis than is assessment with CT. PET is a sensitive tool to assess whether local control has been achieved in patients treated with radiotherapy (1). In patients with ovarian cancer, PET is an accurate diagnostic tool to confirm suspected recurrence, as in the case of increasing CA125 levels during follow-up (1–6). To assess local tumor spread in patients with cervical or endometrial cancer, contrast-enhanced MRI is the most accurate imaging modality for determining parametrial involvement, with an accuracy of 84%–96%, compared with the 55%–80% accuracy of CT (3).

In the routine clinical interpretation of PET/CT images of women, it occurred to us that increased ^{18}F -FDG uptake in the endometrium or ovaries not only may be associated with malignancy but also may be physiologic. To investigate physiologic ^{18}F -FDG uptake in the gynecologic tract, we correlated ^{18}F -FDG uptake in the endometrium and ovaries with menstrual phase and gynecologic history for 285 consecutive women referred for a PET/CT study during a 3-month period.

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For correspondence or reprints contact: Einat Even-Sapir, MD, PhD, Department of Nuclear Medicine, Tel-Aviv Sourasky Medical Center, 6 Weizman St., Tel-Aviv, 64239 Israel.
E-mail: evensap@tasmc.health.gov.il

MATERIALS AND METHODS

Patient Population

A total of 360 women underwent ^{18}F -FDG PET/CT between April and July 2003. Before injection of the radiopharmaceutical, they filled out a questionnaire on their menstrual status, previous gynecologic history, and use of contraceptive and hormonal replacement therapy or antitumor hormonal therapy. Seventy-five of these patients had a previous hysterectomy and were not included in the results analysis. The remaining 285 patients composed the study population and included 246 patients with a nongynecologic malignancy and 39 with a gynecologic malignancy (Fig. 1). The mean age of the study cohort was 50.2 ± 16.9 y, and the range was 14–85 y.

PET/CT

The patients fasted at least 4 h before receiving an intravenous injection of 370–666 MBq (10–18 mCi) of ^{18}F -FDG. Scanning from the base of the skull through the mid thigh was performed using the Discovery LS PET/CT system (GE Medical Systems). First, low-dose CT was performed, with 140 kV, 80 mA, 0.8 s per CT rotation, a pitch of 6, a table speed of 22.5 mm/s, and no specific breath-holding instructions. Immediately afterward, a PET emission scan was obtained without changing the patient's positioning. From 5 to 8 bed positions were used, with an acquisition time of 5 min for each. PET images were reconstructed using an ordered-subsets expectation maximization algorithm. CT data were used for attenuation correction. Studies were read on an eNTEGRA workstation (ELGEMS) equipped with fusion software that enables the display of PET images (with and without attenuation correction), CT images, and the fused data of both modalities.

Assessment of Endometrial Uptake

The uterus was identified on the CT images of the PET/CT study. Uptake of ^{18}F -FDG in the endometrium was measured in the

region corresponding to a hypoattenuating zone detected on CT at the center of the uterus, a finding seen in 110 of 126 perimenopausal patients and in 23 of 159 postmenopausal patients (7). In the absence of this CT finding, endometrial ^{18}F -FDG uptake was best identified on the sagittal PET/CT slices as linear uptake at the center of the uterus. Uptake was expressed as the maximal standardized uptake value (SUV). SUV was automatically obtained on the patient's final report and was calculated as the ratio of activity per cubic centimeter of tissue to the activity in the injected dose per kilogram of patient body weight. SUV was also measured in any focus of ovarian uptake. The presence of a dominant functional ovarian cyst or unsuspected endometrial abnormality on the CT images was recorded.

In patients with known gynecologic malignancy, the location of tumor—in the cervix, endometrium, or ovary—was identified on the CT images and ^{18}F -FDG uptake was measured. In the case of endometrial or cervical cancer, ^{18}F -FDG uptake at the adjacent normal-appearing endometrium was also measured, and the presence of uterine fluid on the CT images was recorded.

Statistical Analysis

The mean SUVs of endometrial ^{18}F -FDG uptake during the various phases of the menstrual cycle in premenopausal patients were assessed and compared. Endometrial uptakes in premenopausal and postmenopausal patients were also compared. The influence of contraceptives (oral or mechanical) and of hormonal therapy was analyzed. Physiologic endometrial uptake was compared with tumor uptake in the cervix, endometrium, and adjacent normal-appearing endometrium. The unpaired *t* test with Bonferroni correction was used for comparison, and $P < 0.05$ was considered statistically significant. Physiologic and malignant increased ^{18}F -FDG ovarian uptakes were compared, and an ROC analysis was performed to identify the SUV that best differentiated between the 2 causes.

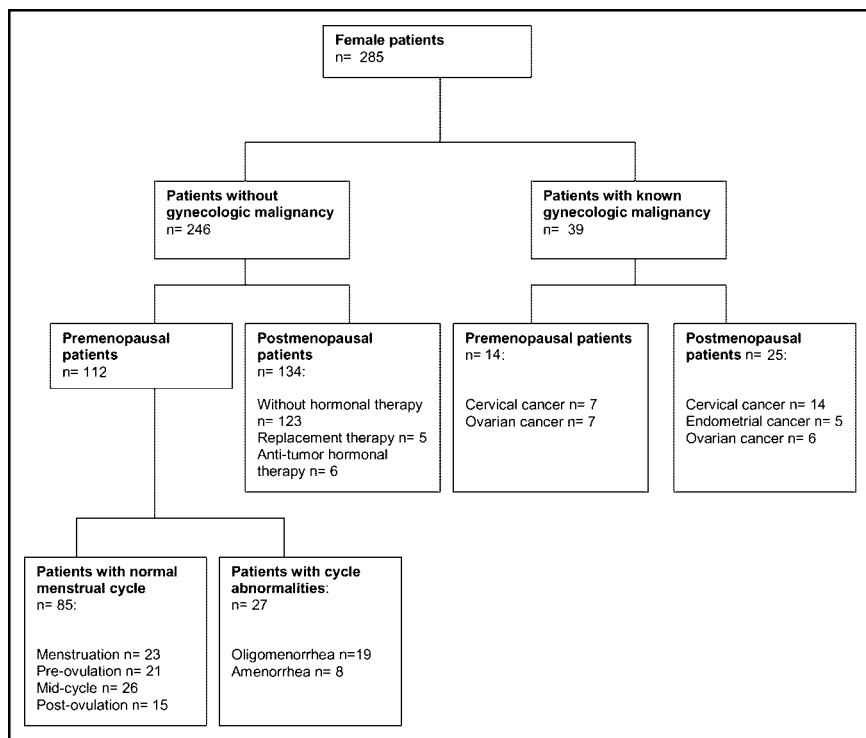


FIGURE 1. Summary of patient population data.

RESULTS

Endometrial Uptake in Patients Without Known Gynecologic Malignancy

Table 1 summarizes the mean SUVs of endometrial ^{18}F -FDG uptake in premenopausal patients according to the cyclic phase at the time of the PET/CT study and the mean SUVs of premenopausal patients with oligomenorrhea or amenorrhea. In premenopausal patients who reported a normal menstrual cycle, the SUVs were statistically higher during menstruation and mid cycle than during the proliferative or secretory phase (menstruation vs. before or after ovulation, $P < 0.01$; mid cycle vs. before or after ovulation, $P < 0.001$). Figure 2 illustrates the 2-peak curve characterizing physiologic endometrial ^{18}F -FDG uptake during a normal menstrual cycle, and Figure 3 displays the increased endometrial uptake in a menstruating patient.

Among the 36 premenopausal patients with a normal cycle who were neither ovulating nor menstruating, 4 had an intrauterine device and 4 were taking oral contraceptives. The 2 contraceptive types were not associated with any significant alteration in the physiologic endometrial SUV (mean, 2.7 ± 0.9 , and range, 1.5–4.2, in patients using an intrauterine device; mean, 2.2 ± 0.6 , and range, 1.3–2.8, in patients using oral contraceptives; mean, 2.6 ± 1.2 , and range, 1.1–5.7, in patients using neither).

In 13 of the 134 postmenopausal patients without a known gynecologic malignancy, the uterus was not identified on the CT image. Of the remaining 121 patients, 116 had ^{18}F -FDG uptake in normal-appearing endometrium on the CT images (11 patients with and 105 without hormonal therapy). The 5 remaining patients had a history of recent curettage with benign findings ($n = 3$), fibroid changes ($n = 1$), or an endometrial polyp ($n = 1$). Table 2 summarizes the endometrial ^{18}F -FDG SUVs measured in postmenopausal patients without known gynecologic malignancies. Patients with benign uterine abnormalities or recent curettage had a higher ^{18}F -FDG uptake than did patients without ($P <$

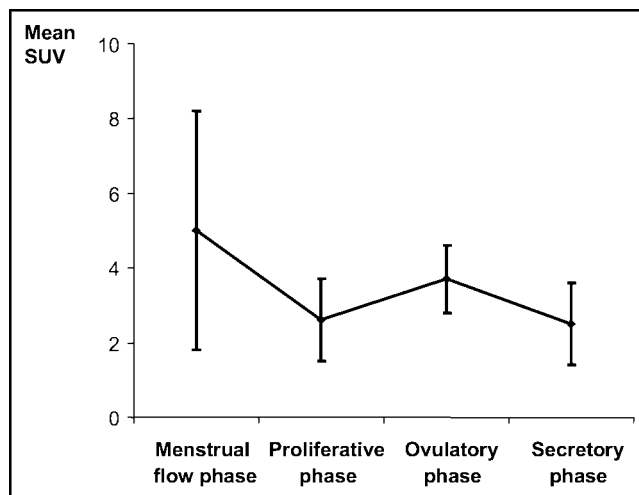


FIGURE 2. Endometrial ^{18}F -FDG uptake (SUV \pm SD) during normal menstruation cycle.

0.001). Hormonal therapy was not associated with a significant alteration in endometrial ^{18}F -FDG uptake. The mean endometrial SUV was 1.7 ± 0.7 (range, 1.1–2.6) in patients receiving hormonal replacement therapy and 1.75 ± 0.5 (range, 1.2–2.6) in patients receiving anti-breast cancer hormonal therapy (not statistically significant).

Among the premenopausal patients with menstrual cycle abnormalities, patients with oligomenorrhea and patients with amenorrhea showed differences. The 2 types of cyclic abnormalities were associated with different mean endometrial SUVs ($P < 0.02$). In patients with oligomenorrhea,

TABLE 1

Endometrial ^{18}F -FDG Uptake in Premenopausal Patients Without Gynecologic Malignancy

Characteristic	No. of patients	SUV \pm SD	
		Mean	Range
Cyclic phase			
Menstrual flow phase	23	5 ± 3.2	2.3–16.6
Proliferative phase	21	2.6 ± 1.1	1.1–5.7
Ovulatory phase	26	3.7 ± 0.9	2–5.4
Secretory phase	15	2.5 ± 1.1	1.3–5.6
Cyclic abnormalities			
Oligomenorrhea	19	3.4 ± 1.4	1.4–6.2
Amenorrhea	8	1.9 ± 1.2	0.9–4.9

SUV was calculated as the ratio of activity per cubic centimeter of tissue to activity in the injected dose per kilogram of patient body weight.

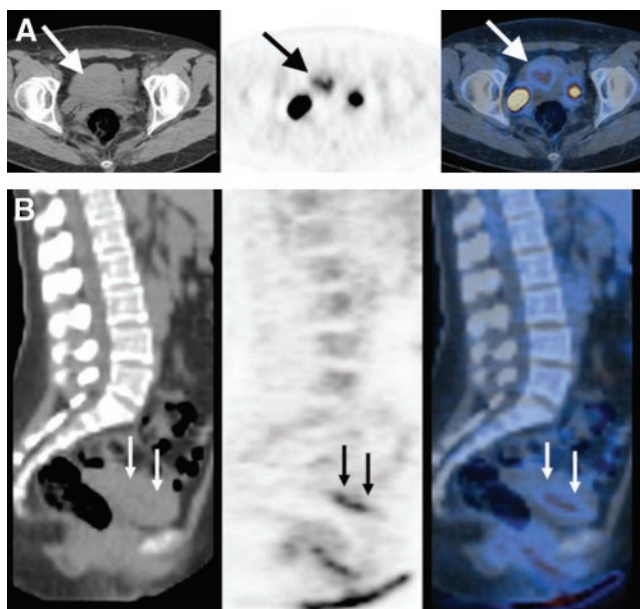


FIGURE 3. Menstruation. (A) Axial PET/CT image shows increased endometrial ^{18}F -FDG (arrows point to endometrial cavity on, from left to right, CT, PET, and fusion images). (B) Sagittal PET/CT image shows a linear increased ^{18}F -FDG uptake in the endometrium (arrows point to endometrial cavity on, from left to right, CT, PET, and fusion images).

TABLE 2

Endometrial ¹⁸F-FDG Uptake in Postmenopausal Patients Without Known Gynecologic Malignancy

Characteristic	No. of patients	SUV ± SD	
		Mean	Range
No hormonal therapy	105	1.7 ± 0.5	0.8–3
Hormonal therapy	11	1.8 ± 0.6	0.9–2.6
Benign uterine pathology	5	4.5 ± 2.1	2.3–8.2

In 13 of the 134 postmenopausal patients, the uterus was not identified on CT. Endometrial SUV was measured in 121 postmenopausal patients without gynecologic malignancy. The SUV was calculated as the ratio of activity per cubic centimeter of tissue to activity in the injected dose per kilogram of patient body weight.

¹⁸F-FDG uptake was high and resembled the values at mid cycle (Table 1), whereas in patients with amenorrhea, endometrial ¹⁸F-FDG uptake resembled the values in postmenopausal patients.

Endometrial Uptake in Patients with Cervical or Endometrial Cancer

The mean SUV was 14.9 ± 7.3 (range, 6.4–29) in 21 cervical tumors and 18.8 ± 9 (range, 7–13.5) in 5 endometrial tumors. In 4 of the 21 patients with cervical cancer, PET/CT images detected tumor invasion to the adjacent body, with a mean SUV of 13.9 ± 7.1 (range, 5.4–24.6), and in the 17 remaining patients the adjacent endometrium appeared normal on CT. Ten of the 17 patients were postmenopausal, and the mean endometrial SUV was 4.7 ± 2.8 (range, 1.4–9), a value significantly higher than that in postmenopausal patients without known gynecologic malignancy ($P < 0.001$). In 5 of those 10 postmenopausal patients, CT detected uterine fluid collection (Fig. 4). The mean endometrial SUV in postmenopausal patients with and without uterine fluid was 6.0 ± 1.9 (range, 3.9–8.2) and 1.9 ± 0.6 (range, 1.4–2.9), respectively ($P < 0.01$). The mean SUV measured in normal-appearing endometrium in premenopausal patients with cervical cancer was 4.8 ± 2 (range, 2.1–9), which is similar to the values in menstruating premenopausal patients without known gynecologic malignancy. All premenopausal patients with cervical carcinoma reported vaginal bleeding. Only 6 of the 21 patients with cervical cancer were referred for surgery. Although endometrial uptake values were higher than in patients without gynecologic malignancy, neither of the operated patients had histopathologic evidence of endometrial invasion.

Increased Ovarian ¹⁸F-FDG Uptake

Increased ¹⁸F-FDG uptake was detected in 28 of the study patients, including 21 premenopausal patients without known gynecologic malignancy and 7 patients with ovarian cancer (6 postmenopausal and 1 premenopausal) (Fig. 5). Increased ovarian uptake was not detected in any of the 134 postmenopausal patients without known gynecologic malig-

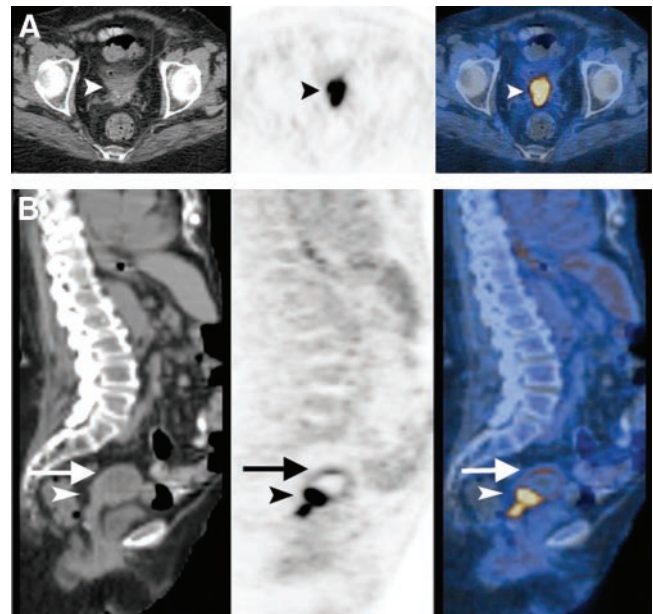


FIGURE 4. Cervical carcinoma. (A) Axial PET/CT image shows intense abnormal ¹⁸F-FDG uptake in the cervical tumor (arrows point to tumor on, from left to right, CT, PET, and fusion images). (B) Sagittal PET/CT image shows the primary cervical tumor (arrowheads on, from left to right, CT, PET, and fusion images) and a distended endometrial cavity surrounded by increased ¹⁸F-FDG uptake and uterine fluid collection. The surgical pathology report showed no evidence of endometrial involvement.

nancy. Fifteen of the 21 premenopausal patients without known gynecologic malignancy and increased ovarian uptake were at the ovulatory phase, and 3 reported having oligomenorrhea. Ovulation was confirmed by the detection of functional ovarian cysts and, occasionally, free fluid at the Douglas pouch on CT. The mean SUV was 5.7 ± 1.5 (range, 3.8–8.2) for nonmalignant ovarian uptake and $9.1 \pm$

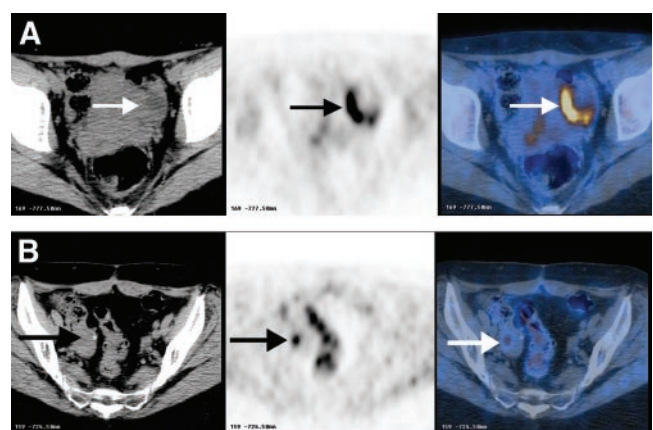


FIGURE 5. From left to right, CT, PET, and fusion images of increased ovarian uptake. (A) Ovulation in a 27-y-old patient. Axial PET/CT image shows increased ¹⁸F-FDG uptake in the margin of a left ovarian functional cyst (arrows). (B) Ovarian cancer in a 56-y-old patient. Axial PET/CT image shows increased ¹⁸F-FDG uptake in the right ovarian tumor (arrows).

4 (range, 4.5–15.6) for ovarian cancer ($P < 0.01$). Receiver-operating-characteristic analysis showed that an SUV of 7.9 separated benign from malignant ovarian uptake with a sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 57%, 95%, 85%, 80%, and 86%, respectively.

DISCUSSION

The normal menstrual cycle reflects the fine balance between the proliferative actions of estrogen and the antiproliferative and secretory transforming actions of progesterone on the endometrium. The cycle consists of the menstrual flow phase; the proliferative preovulatory phase; the mid cycle, or ovulation; and the secretory postovulation phase (8). Glucose phosphorylation is an important rate-limiting step in the estrogenic stimulation of uterine glycolysis. Hughes assessed the activity of endometrial enzymes in 252 patients with normal menstrual histories and found that, in normal endometrial tissue, glycogen synthetase activity causes synthesis of glucose to glycogen in increasing amounts until mid cycle, after which glycogen phosphorylase activity causes the breakdown of glucose during the regressive stage of endometrial activity, with decreased glycogen levels toward the end of the cycle. In patients with abnormal uterine bleeding due to proliferative, hyperplastic, or cancerous endometrium, the normal cycle activity of synthesis and breakdown of glycogen do not occur; a constant glycogen content is retained and tissue energy is created with increase in the activity of glucose-6 phosphate dehydrogenase (9). Increased physiologic endometrial ^{18}F -FDG uptake in a menstruating 40-y-old patient has been previously reported (10). When endometrial ^{18}F -FDG uptake was measured in the current study, 2 peaks of increased physiologic uptake were found in the premenopausal patients with a normal menstrual cycle and no gynecologic malignancy, one at mid cycle and the other at the menstrual flow phase. The fact that a relatively large proportion (24%) of the premenopausal patients in the current study reported menstrual cycle irregularities may be related to previous antitumor treatment in patients referred for a follow-up PET/CT study. Endometrial SUV levels were high, resembling those measured at mid cycle in patients with normal cycles, in the patients who reported oligomenorrhea, whereas the endometrial SUV levels were low, resembling the postmenopausal endometrium, in the patients who reported amenorrhea.

The endometrial uptake values measured in premenstrual patients using oral contraceptives resembled the values measured in nonovulating, nonmenstruating premenopausal patients. These findings probably reflect the effect of oral contraceptives on the endometrium, an effect that includes suppression of glands and resulting in atrophic changes and an almost denuded endometrium (11).

In the majority of postmenopausal patients, some ^{18}F -FDG uptake was measured at the center of the uterus, with

occasional identification of a central hypoattenuating zone. These data correlate with previous morphologic reports suggesting that the postmenopausal endometrium is an active structure and appears to be more in a quiescent state than really in an atrophic condition, particularly during the first few years after cessation of the menstrual cycle (12). Hormone replacement therapy has been reported to be associated with a significantly increased endometrial thickness, compared with the thickness in control subjects, when assessed sonographically. Antitumoral hormonal therapy, such as tamoxifen prescribed for patients with breast cancer, has been associated with a high prevalence of endometrial histopathologic changes such as thickening, glandular hyperplasia, cystic atrophy, and polyps (13,14). Among postmenopausal patients, hormonal therapy was not found to be associated with differences in endometrial ^{18}F -FDG uptake; however, because only a small group of patients were receiving hormonal therapy, its influence on endometrial ^{18}F -FDG uptake remains to be determined in a larger group of patients.

In the assessment of local tumor spread in patients with cervical or endometrial cancer, contrast-enhanced MRI is the most accurate imaging modality for determining parametrial involvement, with an accuracy of 84%–96%, compared with the 55%–80% accuracy of CT (3). Both MRI and CT have been found to overestimate the central tumor volume because of the presence of tissue reaction and edema in the region of tumor–tissue interface (15). Only 6 of 21 patients with cervical carcinoma were referred for surgery. This fact may be explained by the selectivity of the PET/CT patient referral policy, by which only patients with advanced local disease, a high pretest probability for nodal involvement or distant metastases, or suspected metastases on other modalities undergo PET/CT. No direct relationship was found between invasion of the tumor to the adjacent endometrium and high ^{18}F -FDG uptake in the operated patients. High endometrial SUVs were also associated with uterine fluid collection, which may be secondary to cervical stenosis (16). It is possible that a local cytokine environment of the cervical tumor affects the adjacent endometrium, resulting in altered ^{18}F -FDG uptake that is not due to tumor extension (17). Endometrium adjacent to the cervical primary tumor in premenopausal patients showed increased SUVs that were similar to those measured during menstruation in premenopausal patients without gynecologic malignancy. Indeed, all premenopausal patients with cervical cancer reported vaginal bleeding (some referred to this bleeding as menstruation “not on time”). Therefore, it appears that neither coregistration of PET with CT nor measurement of endometrial SUV improves the accuracy of PET/CT in assessing whether a cervical tumor has extended into the uterine body.

Increased ^{18}F -FDG uptake in the ovaries indicated malignancy in postmenopausal patients. In premenopausal patients, however, increased ovarian ^{18}F -FDG uptake could be either malignant or functional. A high SUV (7.9) was found

to be highly specific for malignancy but had a sensitivity of only 57%. Many malignant and functional ovarian lesions had overlapping SUVs. Detecting a dominant functional ovarian cyst on CT and discussing the menstrual cycle phase with the patient may assist in differentiating physiologic from malignant ¹⁸F-FDG ovarian uptake.

CONCLUSION

Dating the menstrual phase in premenopausal patients referred for PET may assist in avoiding a false-positive interpretation of endometrial or ovarian malignancy. Normal uptake of ¹⁸F-FDG in the endometrium of premenopausal patients varies cyclically, being increased at the ovulatory and menstrual phases. Increased uptake in the endometrium adjacent to a cervical tumor does not necessarily reflect uterine tumor invasion. Increased ovarian uptake is associated with malignancy in postmenopausal patients but may be functional in premenopausal patients.

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