Evaluation of FDG PET in Patients with Cervical Cancer

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Although many human cancers can be imaged by 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) and PET, there is little clinical experience with FDG PET in cervical cancer. The purpose of this study was to evaluate the feasibility of FDG PET scans on patients with cervical cancer. **Methods:** FDG PET scans were performed on 21 patients with histologically proven uterine cervical cancer (17 newly diagnosed, 4 recurrence). After two levels of transmission scanning, approximately 370 MBq FDG were injected, and dynamic scans over 60 min were obtained at the level of suspected tumors, followed by static scans. Postvoid scans were also obtained in 11 patients to minimize FDG activity in the urinary bladder. FDG uptake was interpreted visually and classified into 4 grades (0 = normal, 1 = probably normal, 2 = probably abnormal and 3 = definitely abnormal). For a semiquantitative index of FDG uptake in tumors, the standardized uptake value (SUV) corrected by predicted lean body mass (SUL) was calculated and compared. The detectability of lymph node metastases by PET was compared with that by CT. **Results:** Of the 21 newly diagnosed or recurrent cancers, 16 (76%) were detected by FDG PET without use of postvoid imaging (i.e., interpreted as grade 2 or 3). The SULs of tumors ranged from 2.74–13.03, with a mean of 8.15 ± 3.00 (SUV range 3.68–14.94, mean 10.31 ± 3.19). There was no significant relationship between the SUL of cervical cancer and the clinical stage. Postvoid FDG PET images substantially reduced the tracer activity in the urinary bladder and improved the visualization of cervical cancers, with three additional cases detected using the postvoid images. In the 11 patients with postvoid imaging, all 11 cancers (100%) were detected. FDG PET detected lymph node metastases in 6 (86%) of 7 patients with known metastases, whereas CT was positive in 4 patients (57%), equivocal in 2 patients (29%) and negative in 1 patient (14%). All PET and CT scans were true-negative in the patients with no lymph node metastases (interpreted as grade 0 or 1 by PET, and as negative by CT). **Conclusion:** These preliminary data demonstrate the feasibility of FDG PET imaging in patients with cervical cancer. FDG PET appears to be promising for detecting untreated or recurrent cervical cancers and lymph node metastases, although the excreted FDG in the urine remains problematic in some cases.

Key Words: cervical cancer; ^{18}F-fluoro-2-deoxy-D-glucose; PET

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Cervical cancer is the third most common gynecological cancer in the U.S. In 1998, 13,700 new cases and 4,900 deaths due to invasive cervical cancer are expected (*1*). Although the overall mortality from cervical cancer has decreased due to early detection and treatment of preinvasive disease, the mortality of invasive cervical cancer has not changed in 30 y (*1–3*).

The International Federation of Gynecology and Obstetrics (FIGO) classification is used for the clinical staging of cervical cancer (*4*). This is determined by a combination of clinical examination (palpation, biopsy, conization, colposcopy, cystoscopy and sigmoidoscopy) and conventional radiologic examination (chest and bone radiographs, intravenous pyelogram and barium enema). However, clinical staging is not accurate in more advanced disease: 17%–32% inaccuracy for stage IB but 50%–67% inaccuracy for stages II to IV (*5,6*). In advanced cervical cancer, it has been reported that progression-free survival is significantly related to patient age, performance status, paraaortic and pelvic lymph node metastasis and tumor size (*7*). The guidelines for FIGO staging have recently incorporated measurements of tumor size (*8,9*), but they still do not include assessment of another significant prognostic factor: lymph node metastasis.

Although still not recommended in the FIGO staging guidelines, cross-sectional imaging modalities such as CT and MRI have proven to be useful for evaluating morphologic risk factors such as tumor size, depth of stromal invasion, stage of disease and lymph node metastasis. It has been reported that CT has an overall staging accuracy of 58%–88%, but it shows low sensitivity for nodal metastasis (44%), and neither tumor size nor early parametrial invasion can be evaluated reliably (*5,6*). MRI is now considered to be the most accurate imaging method for evaluation of tumor size and of parametrial invasion, and it has shown overall staging accuracy of 80%–92%, whereas the sensitivity for nodal metastasis is similar to CT (50%) (*5*).

Increased glucose metabolism in tumors has been observed (*10*), and many human cancers can be imaged by a glucose analog 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) and PET (*11*). FDG PET has been reported to be useful for differentiating malignant from benign tumors, for staging and for evaluating treatment efficacy in cancer patients

(*12–15*). However, there is little reported clinical experience with FDG PET in cervical cancer.

In contrast to CT or MRI, which both provide primarily morphologic information regarding tumors, PET can noninvasively assess metabolic activity in tumors. Uptake of ^{11}C-methionine in uterine carcinoma has been reported by Lapela et al. (*16*). The purpose of this study was to assess the feasibility of imaging cervical cancer with FDG PET scanning.

MATERIALS AND METHODS

Patients

Twenty-one patients (age range 21–82 y, mean 45 ± 16 y) with histologically proven cervical cancer were studied with FDG PET between May 1993 and May 1997. There were 4 patients with FIGO stage IB, 9 with stage IIB, 7 with stage IIIB and 1 with stage IVA disease. The histologic types were squamous cell carcinoma in 17 patients, adenosquamous cell carcinoma in 3 patients and adenocarcinoma in 1 patient. Patient characteristics are shown in Table 1. Of the 21 patients, 17 had newly diagnosed cervical cancer, and the other 4 had recurrent cervical cancer after treatments, which included radical hysterectomy with pelvic lymph node dissection in 1 patient (patient 17), radical hysterectomy with pelvic lymph node dissection followed by external radiation therapy and cisplatin-based chemotherapy in 1 patient (patient 1) and external radiation therapy followed by brachytherapy with cesium implants and cisplatin-based chemotherapy in 2 patients (patients 2 and 3). The mean duration from the last treatment to the PET study was 10 mo. Written informed consent was obtained from all patients for the study, which was approved by the institutional review board and conducted under the guidelines for a physician-sponsored investigational new drug exemption for FDG.

For evaluating FDG uptake in the normal uterus, PET images in 14 female patients (age range 35–83 y, mean 56 ± 15 y) who underwent PET studies for other cancers (bladder cancers in 5, colorectal cancers in 5 and ovarian cancers in 4 patients) were also assessed qualitatively and quantitatively.

PET Scanning

FDG was produced by a standard nucleophilic fluorination method as previously described (*17*). FDG PET scans were performed with a model 921 EXACT (47 scanning planes, 15-cm longitudinal field of view [FOV]) scanner (CTI, Knoxville, TN, distributed by Siemens Medical Systems, Iselin, NJ). The reconstructed x-y resolution with the Hanning filter cutoff value of 0.3 was approximately 1.2 cm full width at half maximum. All patients fasted for at least 4 h before PET scanning. Two levels of transmission scans (at least 10 min per each scan) were obtained using a ^{68}Ge rod source for the purpose of attenuation correction, followed by intravenous tracer injection (approximately 370 MBq FDG). Sequential dynamic scans at the level of suspected tumors were obtained through 60 min. These dynamic scans were generally six 10-s scans, three 20-s scans, two 90-s scans, one 5-min scan and five 10-min scans. After completion of sequential dynamic scans, static scans were obtained at the upper level to evaluate for possible lymph node metastasis. Then, patients were instructed to void, and the postvoid emission and transmission scans, each of

TABLE 1
Patient and Tumor Characteristics

		Primary tumor					Lymph node				
				PET finding			PET finding				
Patient no.	Age (y)	Histology	Stage (FIGO)	Grade	P-void	SUL	Grade	SUL	Location	CT finding	Final diagnosis
1	21	asc (rec)	IB	1	NA	NA	2, 3	2.14, 2.94	Pelvis, para-aorta	Positive	Metastasis
2	43	ac (rec)	IIB	2	NA	2.74	1	NA	Pelvis	Positive	Metastasis
3	41	scc (rec)	IIB	3	NA	6.74	3	2.38	Pelvis	Negative	Metastasis
4	28	scc	IIB	3	NA	13.03	0	NA		Negative	No metastasis
5	55	scc	IIB	2	3	4.27	1	NA	Pelvis	Negative	No metastasis
6	63	asc	IIB	1	2	NA	0	NA		Negative	No metastasis
7	38	asc	IIB	3	NA	9.41	0	NA		Negative	No metastasis
8	37	scc	IVA	3	NA	10.28	2, 2	2.49, 2.52	Pelvis, para-aorta	Equivocal	Metastasis
9	49	scc	IIIB	3	3	7.69	2	2.65	Pelvis	Negative	Not confirmed*
10	58	scc	IIB	1	NA	NA	0	NA		Negative	No metastasis
11	35	scc	IIIB	3	NA	9.60	2	3.24	Pelvis	Positive	Not confirmed*
12	35	scc	IIB	3	3	10.85	1	NA	Para-aorta	Equivocal	Not confirmed*
13	48	scc	IIIB	3	3	5.52	2, 2	2.73, 2.49	Pelvis, para-aorta	Positive	Metastasis
14	82	scc	IB	1	2	NA	0	NA		Negative	No metastasis
15	35	scc	IIIB	3	3	11.73	2	4.25	Pelvis	Equivocal	Metastasis
16	33	scc	IIIB	3	NA	5.11	3	3.15	Pelvis	Positive	Metastasis
17	26	scc (rec)	IB	3	3	6.41	0	NA		Negative	No metastasis
18	52	scc	IIIB	3	3	11.84	0	NA		Negative	No metastasis
19	42	scc	IIIB	3	3	8.89	1	NA	Pelvis	Negative	No metastasis
20	48	scc	IB	3	NA	6.34	1	1.95	Pelvis	Equivocal	Not confirmed*
21	77	scc	IIB	1	2	NA	0	NA		Negative	No metastasis

*Metastasis was not confirmed, but radiation therapy was performed.

FIGO = International Federation of Gynecology and Obstetrics; p-void = postvoid; SUL = standard uptake value lean; asc = adenosquamous cell carcinoma; rec = recurrence; NA = not available; ac = adenocarcinoma; scc = squamous cell carcinoma.

10-min duration, were obtained over the pelvic regions. Generally, two levels 30 cm of FOV) of scanning were imaged from the level of symphysis pubis to the level of middle abdomen. In general, CT was not available at the time of PET and not used to guide patient positioning for PET scans. Software used to perform the postinjection emission and transmission scans was provided by Siemens/CTI. Images were reconstructed using filtered backprojection.

CT Scanning

CT scans were obtained with 10-mm-thick contiguous axial sections with a GE-9800 scanner (Hi-lite Advantage; GE Medical Systems, Milwaukee, WI) in all but 2 patients (CT scans of patients 1 and 2 were performed at outside hospitals). Intravenous contrast material (Omnipaque-300; Winthrop Pharmaceuticals, New York, NY) and oral contrast material (1.5% Hypaque solution; Winthrop Pharmaceuticals) were used. The duration from the CT scans to the PET scans ranged from 1–67 d (mean 15 d).

Image Analysis

All PET and CT scans were interpreted separately. All PET images were analyzed on an interactive computer display by two observers who were blinded to other imaging results, but unblinded to the clinical information of previous treatments, such as surgical procedures before the PET scans. Any obvious foci of increased FDG uptake were evaluated using transaxial, sagittal and coronal displays and compared between prevoid and postvoid scans, if available. We also assessed the sequential images of dynamic scanning if we appreciated indeterminate uptake in prevoid or postvoid scans, to differentiate the uptake in the tumor or lymph nodes from that in the blood and urinary tract. Thus, FDG uptake in the last (50–60 min) frames of dynamic scans and static scans was assessed visually, and the degree of abnormality of FDG accumulation was classified into four grades by the consensus interpretations: 0 = normal, 1 = probably normal, 2 = probably abnormal and 3 = definitely abnormal for both sets of images. For a semiquantitative index of FDG uptake in tumors, we defined standardized uptake value lean (SUV-lean [SUL]), which is decay-corrected tissue activity divided by the injected dose per patient body weight corrected by predicted lean body mass, as described previously (*18*). SULs were calculated from regions of interest (ROIs) that were placed by means of automated algorithm on the maximal area (16 pixels in size) of FDG uptake within a larger ROI covering the tumors. No correction was applied for partial volume effects.

CT scans were analyzed on film separately, whereas the official reports were referred to in the patients whose CT was performed in the outside hospitals (patients 1 and 2). Standard CT size criteria for individual lymph nodes were used (>1 cm length in the short axis was interpreted as positive for metastasis). Enlarged lymph nodes on CT scans within the area examined with PET were classified into these categories: positive (size in short axis >1 cm), equivocal (= 1 cm) and negative (<1 cm).

Final diagnosis for the status of lymph node metastasis was obtained by surgical resection or by clinical follow-up, including imaging studies such as follow-up CT. Biopsy results, physical examination and other correlative imaging studies were assessed for primary lesion diagnosis.

RESULTS

Sixteen (76%) of 21 cervical cancers were detected by FDG PET without using postvoid images (i.e., interpreted as grade 2 or 3), although the intensity of FDG uptake varied and the SULs of tumors ranged from 2.74 to 13.03 with a mean of 8.15 ± 3.00 (Table 1). If we calculated SUV, the SUVs of cervical cancers ranged from 3.68 to 14.94 with a mean value of 10.31 ± 3.19. In 5 patients, obvious FDG uptake in tumors was difficult to detect because of the intense excreted FDG activity in the urinary bladder. Postvoid images substantially reduced the tracer activity in the urinary bladder and improved the visualization of cervical cancers (Fig. 1). In 3 additional patients, tumors were detected with the postvoid scans. In all 11 patients in whom postvoid imaging was performed, the primary cervical cancer was detected. The sequential images of dynamic scanning were also helpful, if we appreciated indeterminate uptake in prevoid or postvoid scans. There was no significant relationship between the SUL of cervical cancer and the clinical stage (Fig. 2).

Lymph node metastasis was confirmed surgically in 1 patient and by clinical follow-up, including follow-up CT, in 6 patients (Table 1). FDG PET detected lymph node metastases (nine locations in total) in 6 (86%) of 7 patients, whereas CT was positive in only 4 patients (57%), equivocal in 2 patients (29%) and negative in 1 patient (14%). The apparent SULs of the metastatic lymph nodes ranged from 2.14 to 4.25 (SUVs range 2.14–6.81). Representative cases are shown in Figures 3, 4 and 5. In 1 patient (patient 2) with a false-negative PET scan (interpreted as grade 1), obvious

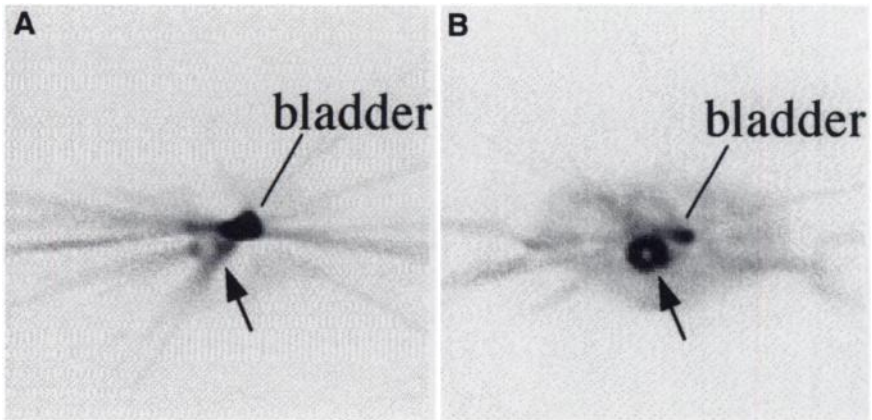

FIGURE 1. Prevoid (A) and postvoid (B) FDG PET images of patient with cervical cancer (patient 18). Postvoid image substantially reduced tracer activity in urinary bladder and improved visualization of cervical tumor (arrow).

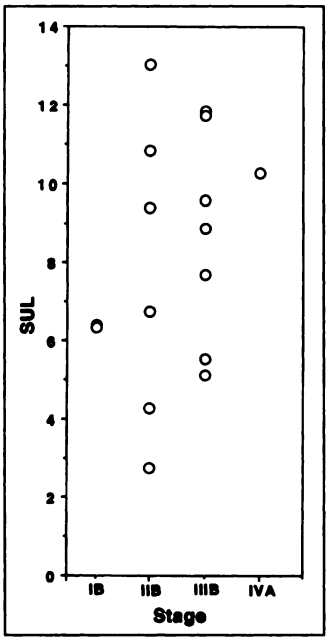

FIGURE 2. Relationship between SUL of cervical cancer and clinical (FIGO) stage.

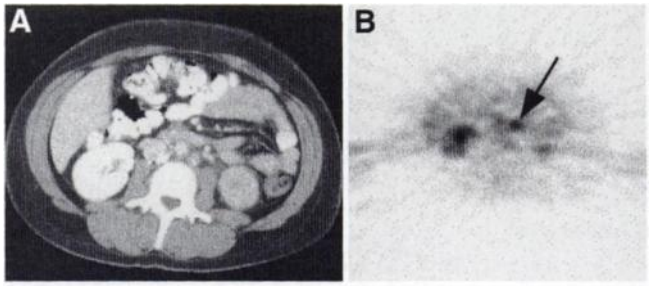

FIGURE 4. Contrast-enhanced CT image (A) and FDG PET image (B) of 37-y-old woman with cervical cancer and lymph node metastasis (patient 8). Although CT shows equivocal-sized (1 cm in diameter) para-aortic lymphadenopathy, PET image clearly shows intense focal FDG accumulation in lymph node (arrow). Metastasis was confirmed by follow-up CT.

(in retrospect) FDG uptake in the metastatic lymph node was difficult to detect because of the intense excreted FDG accumulation in the adjoining ureter. On the other hand, in 10 patients with no lymph node metastasis, all PET and CT scans correctly excluded the presence of lymph node metastasis (interpreted as grade 0 or 1 by PET, and as negative by CT). In 2 patients (patients 5 and 19), the initial prevoid PET scans showed focal intense FDG uptake in the pelvic cavity, but these foci of uptake disappeared on the postvoid scans. Thus, both observers considered these foci of uptake to represent excreted urine activity in the ureters (interpreted as grade 1). In the other 4 patients, although lymph node metastases were suspected by PET or CT, final histologic diagnoses were not obtained, because radiation therapy, including to the area of the suspected lymph node metastases, was performed after these CT/PET scans.

By contrast, in the control group of patients, all with presumed normal uteri, no obvious FDG uptake (interpreted as grade 0) was observed in 11 of 14 patients, and faint FDG

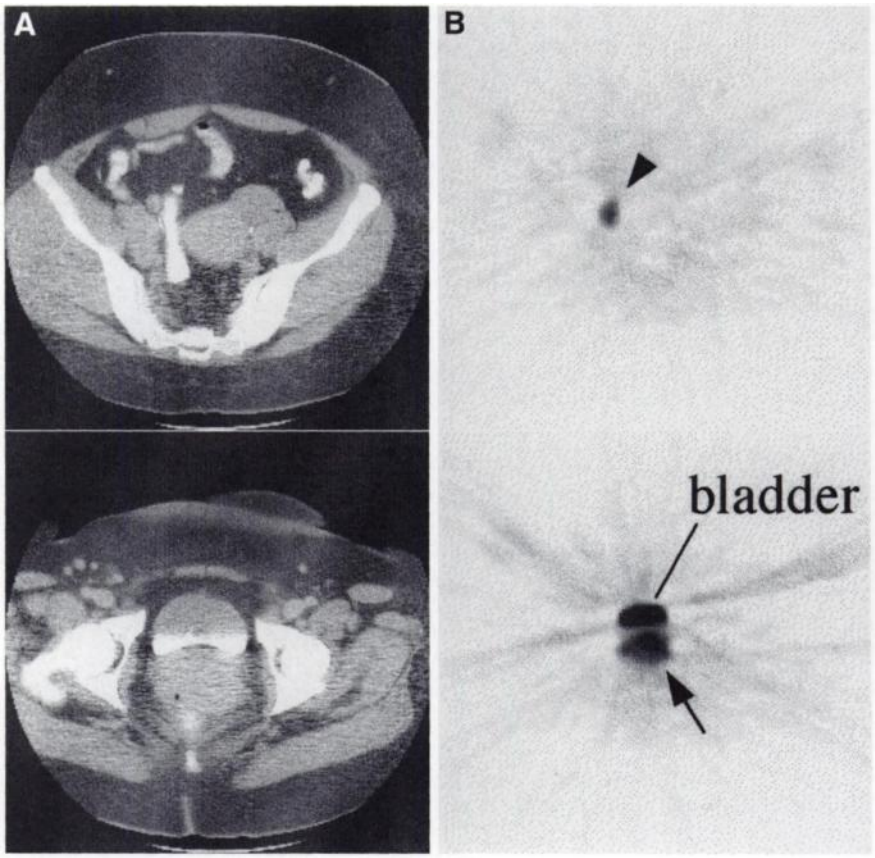

FIGURE 3. Contrast-enhanced CT images (A) and FDG PET images (B) of 33-y-old woman (patient 16) with cervical cancer and lymph node metastasis. Both primary cervical cancer (arrow) and right intrapelvic lymph node metastasis (arrowhead) show intense FDG uptake.

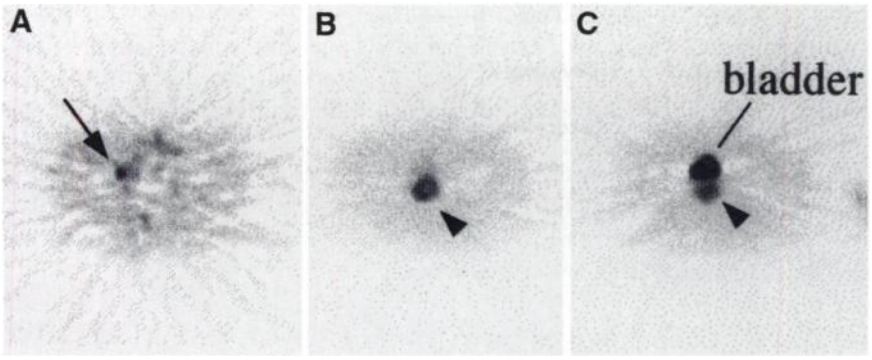

FIGURE 5. FDG PET images of 41-y-old woman with recurrent cervical cancer and lymph node metastasis (patient 3). Although CT did not detect any lymph node metastasis, PET demonstrates focal intense FDG uptake in right pelvis (arrow, A), in addition to uptake in recurrent tumor (arrowheads, B and C). Recurrent tumor and right intrapelvic lymph node metastasis were confirmed surgically.

uptake (interpreted as grade 1 or 2) was observed in the other 3 patients (aged 36, 47 and 55; maximal SUL of 1.76, 2.63 and 2.14, respectively).

DISCUSSION

Cross-sectional imaging such as CT and MRI has become widely used for evaluating morphologic aspects of tumors, such as tumor size, parametrial invasion and lymph node metastasis in cervical cancers (*5,6*). Metabolic imaging of cervical cancer is not well studied, although tissue studies have shown significantly increased enzymes of glucose metabolism in cervical cancers when compared with the normal cervix (*19*). In this study, we showed that newly diagnosed and recurrent cervical cancers and lymph node metastases could be imaged well with FDG PET in many instances.

In contrast to CT or MRI, both of which provide morphologic information regarding tumors, FDG PET noninvasively assesses metabolic activity in tumors. In this study, we calculated tumor SUL, for a more weight-independent index of SUV (*18*). SULs of cervical cancers varied widely (range 2.74–13.03) and showed no significant correlation to the clinical staging. These results were partly in agreement with the previous results of variations in enzyme (hexokinase) activity (*19*), metabolic parameters (adenosine triphosphate, glucose, lactate) (*20*) and ^{11}C-methionine PET studies (*16*). However, because reports that the intensity of FDG uptake in tumors may in some instances be related to the proliferative activity (*21,22*), whereas, in in vitro studies, FDG uptake rather directly correlated with the number of viable cancer cells (*23*), SUL could potentially be a quantitative index for diagnosing the aggressiveness of tumors or for predicting patients' prognosis, as previously reported in some other human cancers (*24,25*). Moreover, because metabolic changes could precede morphologic changes after effective treatments, they could potentially be early and reliable indices for assessing treatment response, as previously reported in breast and other cancers (*13,26*). On the other hand, in some situations after treatment (such as after radiation implants), the assessment of treatment efficacy seems to be difficult with CT or MRI. Evaluation of FDG uptake in cervical cancers in much larger numbers of patients is needed, and it will also be essential to compare tumor FDG uptake before and after treatment.

We evaluated normal uterine FDG uptake in 14 patients with other cancers, and there was no obvious FDG uptake in 11 patients. Although faint FDG uptake in the uterus were observed in 3 patients, those SULs were lower than those in cervical cancers. Lapela et al. (*16*) reported that normal endometrial ^{11}C-methionine uptake was lower than that present in cervical or endometrial cancers. Spellman et al. (*27*) reported elevation of endometrial enzymes (including hexokinase) during the secretory phase; however, Marshall et al. (*19*) reported there were no significant differences in enzyme activity between secretory and proliferative phases. It has been reported that substantially increased uterine vascularity was generally observed in the secretory and menstrual phases by radionuclide imaging (*28*). In vivo, FDG uptake could be altered by blood flow, transport and enzyme (hexokinase) activity, therefore FDG uptake in normal uterus could be altered by the phase of menstrual cycle. Preclinical studies have shown that FDG uptake in the estrogen stimulated uterus is significantly greater than if no stimulation is present (*29*). Recently, a case of intrauterine accumulation of FDG during menstruation was reported (*30*). The aforementioned ^{11}C-methionine study (*16*) also reported that normal endometrial uptake was slightly higher in the secretory phase than in the proliferative phase, although only a small number of patients (n = 4) were assessed. Because relatively older and relatively small numbers of patients with presumed normal uteruses were assessed in our study and the information regarding menstrual cycle was not tabulated, the full range of normal uterine FDG uptake and menstrual effect on uterine FDG uptake are still incompletely resolved.

The accuracy of detecting lymph node metastasis by CT or MRI is dependent on the size of the lymph node on the cross-sectional images. Lymph node sizes greater than 1 cm in the short axis have been generally considered abnormal (*31*), but the sensitivities of CT and MRI are still low (reported as approximately 50%) (*5,6*). In the current study, PET showed 86% sensitivity and 100% specificity (80%, if postvoid scans were not available), whereas CT showed 57% sensitivity (up to 86%, if equivocal scans were

interpreted as positive) and 100% specificity. We suggest that metabolic assessment by FDG PET could increase the accuracy for detecting lymph node metastasis in patients with advanced-stage cervical cancer, especially if combined with morphologic information provided by CT. Indeed, morphologic information by CT (or MRI) appears to be helpful to ensure accurate localization of the increased foci of FDG uptake found in the PET images.

In colorectal cancer, Strauss et al. (*12*) previously reported the usefulness of FDG PET for differentiating postoperative recurrence from scar, with results superior to CT. Anzai et al. (*32*) reported that FDG PET was significantly more accurate than CT or MRI in detecting recurrence of head and neck cancers, where it was difficult because of the distorted anatomy (after surgery or radiation therapy). In staging of mediastinal lymph node involvement in patients with lung cancer, Wahl et al. (*14*) reported that FDG PET showed 81% accuracy, whereas CT showed only 52% accuracy, and they also reported that FDG PET had the capability to detect tumors in some normal-sized lymph nodes and to exclude tumor involvement in some enlarged lymph nodes. Similar observations have also been reported in breast cancer, melanoma and other cancers (*15,33,34*). Our current results in cervical cancer suggest the similar ability of FDG PET for detecting tumors and lymph node metastases not clearly depicted by anatomic imaging methods. Thus, although neither CT/MRI nor FDG PET is perfect for detecting tumors and lymph node metastases, PET has the capability to add useful functional information in the clinical setting. The advantages of PET are expected to be most apparent in cases of distorted anatomy (recurrence after surgery or radiation therapy) or in normal-sized lymph nodes, where anatomic imaging has its limitations.

In this study, we obtained postvoid FDG PET scans in 11 patients. All postvoid images substantially reduced the tracer activity in the urinary bladder and improved the visualization of cervical tumors. With postvoid imaging, our sensitivity in lesion detection was 100%. Moreover, these postvoid scans were helpful to differentiate the abnormal foci of FDG uptake from the physiologically intense FDG uptake in the excreted urine and, thus, improved accuracy for detecting nodal metastases. Therefore, this approach appears very helpful for lesion detection in the pelvis. In another method for possibly reducing FDG activity in the urinary bladder, Kosuda et al. (*35*) used retrograde saline irrigation by placing a multilumen Foley catheter for evaluating bladder cancer by FDG PET. However, they reported that there were 4 of 12 (33%) false-negative FDG PET scans and that urinary activity near or overlying tumor activity was the norm for primary lesions. Although intravenous drip infusion of saline and diuretics could be useful for reducing or diluting FDG activity in the urine (*36*), postvoid imaging was quite helpful in our preliminary experience. Recently, Leisure et al. (*37*) have reported that the combination of hydration and administration of furosemide with retrograde saline irrigation was useful for imaging of the abdomen and pelvis. They also underscored the usefulness of postvoid scanning for distinguishing pathologic findings from physiologic structures such as bladder diverticula. Although the aforementioned methods can reduce FDG activity in the urinary system and improve the tumor visualization, intense excreted FDG uptake in the urine still appears to be a major pitfall for evaluating lesions near the ureter. Despite this limitation, FDG and PET offer considerable promise for imaging cervical cancer.

CONCLUSION

These preliminary data indicate the feasibility of FDG PET imaging of cervical cancer. Although our study population was limited in size and estimates of accuracy of the method are not yet robust (as not all patients had histologic proof of all lesion sites), our data suggest FDG PET has considerable potential for noninvasively detecting lymph node metastasis in patients with advanced-stage cervical cancer and appears superior to CT. Although postvoid scanning improved the visualization of cervical cancers, intense excreted FDG accumulation in the urine remains a challenging confounding factor. Further prospective evaluation of FDG PET in larger numbers of patients with cervical cancer is warranted to more precisely define its accuracy, as well as studies to assess treatment response.

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