Detection of Early Recurrence with ^{18}F-FDG PET in Patients with Cervical Cancer

Sang-Young Ryu, MD[1]; Moon-Hong Kim, MD[1]; Suck-Chul Choi, MD[1]; Chang-Woon Choi, MD[2]; and Kyung-Hee Lee, MD[1]

[1]Department of Obstetrics & Gynecology, Korea Cancer Center Hospital, Seoul, Korea; and [2]Department of Nuclear Medicine, Korea Cancer Center Hospital, Seoul, Korea

This study investigated the feasibility of PET with ^{18}F-FDG to evaluate retrospectively early recurrence in patients with cervical cancer. **Methods:** From September 1997 to March 2000, 249 patients with no evidence of cervical cancer after treatment were investigated with ^{18}F-FDG PET. ^{18}F-FDG PET scanning, beginning 50 min after injection of 370–555 MBq ^{18}F-FDG, was performed. ^{18}F-FDG uptake other than physiologic uptake was evaluated with the standardized uptake value and was analyzed by 2 observers who were unaware of CT or MRI data. CT or MRI and needle biopsies were performed to evaluate the positive lesions on ^{18}F-FDG PET, and all patients were monitored closely for 6 mo for recurrence. **Results:** Of the 249 patients, 80 patients (32.1%) showed positive lesions with ^{18}F-FDG PET, and 28 patients (11.2%) were clinically or histologically confirmed as having recurrences. Eighty-two percent of recurrence was detected within 6–18 mo after diagnosis, and 89% of recurrence occurred in Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIb and stage III patients. The sensitivity and specificity of ^{18}F-FDG PET for detection of early recurrence were 90.3% and 76.1%, respectively. The sensitivity of ^{18}F-FDG PET was high in mediastinal, hilar, and scalene lymph nodes, spine, and liver; however, the sensitivity was relatively low in lung, retrovesical lymph nodes, and paraaortic lymph nodes. Three false-negative cases were detected in lung, retrovesical lymph nodes, and paraaortic lymph nodes. **Conclusion:** ^{18}F-FDG PET was effective in detecting early recurrences in cervical cancer patients with no evidence of disease. ^{18}F-FDG PET may be a useful follow-up method for cervical cancer, thereby providing the patients with early opportunities for sophisticated treatments.

Key Words: ^{18}F-FDG PET; cervical cancer; recurrence

J Nucl Med 2003; 44:347–352

Cervical cancer is one of the most common gynecologic malignancies throughout the world. Although the overall mortality from cervical cancer has decreased because of early detection and treatment of preinvasive disease, it still remains one of the leading causes of cancer death (*1*). Despite of carefully planned and executed treatments, approximately 30% of cervical cancer is known to eventually recur after treatment (*2*). Conventional follow-up methods, such as physical examination, Papanicolaou smear (Pap smear), and tumor markers, and radiologic imaging methods, such as CT or MRI, have been used to detect early recurrence; however, it is very difficult to achieve an early diagnosis of pelvic recurrence of cervical cancer (*3*).

PET with ^{18}F-FDG, which is preferentially trapped in tumor cells, reveals a functional image of high glucose metabolism (*4,5*). Recently, ^{18}F-FDG PET has been widely used for detection of early recurrence that cannot be diagnosed with conventional radiologic imaging studies and is known to be more accurate than CT or MRI in detecting recurrent lymph node metastases in several human cancers (*6*). In lung cancer, ^{18}F-FDG PET showed 81% accuracy on the involvement of mediastinal lymph nodes, whereas CT showed only 52% accuracy (*7*). Similar observations have also been reported in breast cancer, melanoma, and other cancers (*8,9*).

In cervical cancer, the role of ^{18}F-FDG PET has not been well established. Recently, Sugawara et al. (*10*) reported that ^{18}F-FDG PET could detect 100% of cancers and 86% of lymph node metastasis, whereas CT was positive in 57% of lymph node metastasis in 21 cervical cancers, suggesting a promising role of ^{18}F-FDG PET in cervical cancer detection. In other studies, ^{18}F-FDG PET is known to be very effective not only in detecting early recurrences but also in preoperative staging and evaluating the response of treatment (*11–17*). However, the feasibility of ^{18}F-FDG PET in the early detection in cervical cancer recurrence is not well established.

The purpose of this study was to assess the feasibility of ^{18}F-FDG PET in detecting early cancer recurrences in patients with no evidence of the ailment unmasked by conventional imaging methods.

MATERIALS AND METHODS

Patients

From September 1997 to March 2000, 249 patients with cervical cancer, showing no evidence of disease after treatment, under-

went ^{18}F-FDG PET as part of their investigations. The patients had histologically proven cervical cancers and were treated with surgery or radiation combined with or without chemotherapy according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) clinical stage. The detection rate of ^{18}F-FDG PET for recurrences was analyzed retrospectively.

All patients were treated and monitored according to standard protocol. In brief, most of the patients with stage Ib and stage IIa were treated with radical hysterectomy and bilateral pelvic lymphadenectomy. Postoperative adjuvant radiation therapy was performed on patients with high-risk factors such as full-thickness involvement of the cervix, parametrial invasion, lymphatic invasion, and positive resection margin. Definitive radiation therapy without (before 1999) or with (after 1999) chemotherapy was performed on patients with stage IIb or higher, and chemotherapy was performed on patients with distant metastasis. The chemotherapy regimen was based mainly on cisplatin, such as 5-fluorouracil (500 mg/m^2) + cisplatin (50 mg/m^2) or cyclophosphamide (500 mg/m^2) + cisplatin (50 mg/m^2). After treatment, patients were monitored every 3 mo in the first 2 y and every 6 mo thereafter for 5 y with tumor markers, Pap smears, chest radiography, and annual pelvic CT or MRI.

In patients who had undergone surgery, no evidence of disease was defined as normal follow-up tests, including physical examination, chest radiography, tumor marker (squamous cell carcinoma antigen), Pap smear, and annual radiologic imaging studies. In patients who were treated with radiation, those who showed complete disappearance of the lesion on radiologic imaging studies performed at least after 6 mo of treatment and who showed normal follow-up tests (described above) were defined as having no evidence of disease.

^{18}F-FDG PET was recommended as a part of the work-up on all patients with high risk factors for recurrence such as full-thickness involvement of the cervix, parametrial invasion, lymphatic invasion, and positive resection margin. Among them, 249 patients, who showed no evidence of disease on previous annual pelvic CT or MRI, physical examination, chest radiography, tumor marker, and Pap smear, were selected retrospectively for analysis.

PET

Patients were prepared with overnight fasting before ^{18}F-FDG injection. ^{18}F-FDG PET was performed on an Advance HR+ scanner (General Electric, Waukesha, WI), starting 50 min after injection of 370–555 MBq (10–15 mCi) ^{18}F-FDG with the bladder emptied by Foley catheter insertion and injection of diuretics to reduce tracer activity in the bladder.

^{18}F-FDG PET images were interpreted by using a dedicated system (ECAT EXACT 921; Siemens/CTI, Knoxville, TN) with a 10.8-cm transverse field of view and a 2-dimensional acquisition mode. Three- to 5-min transmission scans and 8-min emission scans were obtained. Five or 6 bed positions were used to cover the area from the orbitomeatal line to the midfemoral line. Images were reconstructed on transaxial, sagittal, and coronal planes by means of the ordered-subset expectation maximization algorithm and segmented photon absorption correction and were interpreted by 2 observers on both film and computer displays, who were unaware of the clinical information of previous treatment and of annual CT or MRI data. Any focal uptake of ^{18}F-FDG, which is considered not be physiologic on PET images, was measured on the basis of the standardized uptake value, being the radioactive

concentration in a hot spot divided by the injected dose and the patient's body weight.

Diagnosis of Recurrence

Any positive lesion on ^{18}F-FDG PET was evaluated with CT or MRI and was confirmed for recurrence histologically by fine-needle aspiration (FNA) as quickly as possible. For the lymph nodes in the mediastinum, hilum, paraaorta, and pelvis, lymph nodes of >1 cm in the short axis on CT were interpreted as positive for metastasis. Lymph nodes that had prominent uptake on ^{18}F-FDG PET but were <1 cm in the short axis were reevaluated with CT 3 mo later. If there was no change in the size on the follow-up CT scan, the patients were recommended to follow-up every 3 mo for 1 y. All scalene lymph nodes with obvious ^{18}F-FDG uptake were evaluated for recurrence with FNA or node dissection.

Any prominent lesion in the lung parenchyma on ^{18}F-FDG PET was evaluated for recurrence with chest CT and histologically confirmed by FNA or lung biopsy. Small lung lesions of <0.5 cm, which were difficult to access with FNA, were evaluated with CT 3 mo later. If there was no change in the size on the follow-up CT scan, the patients were recommended to follow-up every 3 mo for 6 mo.

In other body regions such as the retrovesical area, liver, and chest wall, any lesion of >1 cm in size on CT was confirmed by FNA. A prominent uptake on ^{18}F-FDG PET of <1 cm in the short axis was reevaluated with CT 3 mo later. If there was no change in size on the follow-up CT scan, the patients were recommended to follow-up every 3 mo for 6 mo.

CT or MRI images to confirm recurrences were analyzed by 2 separate observers, who were unaware of ^{18}F-FDG PET data and clinical information. If there was no histologic evidence of recurrence, we decided there was no evidence of disease after close follow-up for 1 y.

RESULTS

The median age of the patients was 51 y (range, 31–78 y), and 59.7% of the patients were classified as FIGO stage Ib and stage IIa. Histologically, 90.7% of the cervical cancer was squamous cell carcinoma. The duration of no evidence of disease at the point of ^{18}F-FDG PET was not statistically different in stages Ib, IIa, and IIb; however, ^{18}F-FDG PET scans were obtained earlier in patients with stage III than in patients with other stages. The median interval from the last CT or MRI to ^{18}F-FDG PET was 6 mo (Table 1).

Of the 249 patients with cervical cancer who showed no evidence of disease after treatment, 80 patients (32.1%) showed positive lesions on ^{18}F-FDG PET (Table 2). Among the 80 patients with positive ^{18}F-FDG PET scans, 28 patients (11.2% [28/249 patients]) were clinically or histologically confirmed to have recurrent lesions (Fig. 1). The sensitivity and specificity of ^{18}F-FDG PET in detecting recurrences of cervical cancer were 90.3% and 76.1%, respectively. Positive and negative predictive values of ^{18}F-FDG PET in detecting recurrence of cervical cancers were 35% and 98.2%, respectively.

Most recurrences were detected within 18 mo after diagnosis of the disease, and the peak period of detection was 9–12 mo after diagnosis (Fig. 2). The detection rate of

TABLE 1
Patient Characteristics

Characteristic	Value
No. of patients	249
Age (y) (range)	51 (31–78)
Stage*	
Ib	100 (40.1)
IIa	49 (19.6)
IIb	83 (33.3)
III or IV	17 (6.8)
Histology*	
Squamous	226 (90.7)
Adenocarcinoma	10 (4)
Adenosquamous	5 (2)
Other†	8 (3.2)
Treatment*	
Surgery	86 (34.5)
Radiation	90 (36.1)
Surgery + radiation	68 (27.3)
Chemotherapy	5 (2)
Median duration of ^{18}F-FDG PET from last CT or MRI (mo) (range)	6 (3–12)
Median duration of NED (mo) (range)	30 (6–282)
Ib	30 (7–129)
IIa	35 (7–108)
IIb	31 (6–282)
III or IV	16 (6–165)

*Values in parentheses are percentages.
†Six undifferentiated, 1 clear, and 1 glassy cell.
NED = no evidence of disease.

^{18}F-FDG PET according to the stage was higher in FIGO stages IIb and III than in stages Ib and IIa (20.4% and 29.4% vs. 6% and 6.1%, respectively) (Fig. 3).

The sensitivity of ^{18}F-FDG PET was relatively high in lesions such as the mediastinum, hilum, chest wall, scarlene lymph node, iliac, spine, and liver; however, it was relatively low in lesions including the lung, retrovesical area, and paraaortic lymph node. The specificity of ^{18}F-FDG PET was relatively low in lesions such as the lung, retrovesical lymph node, and paraaortic lymph node (Table 3). Incidentally, as shown in Figure 4, ^{18}F-FDG PET detected 2 cases each of thyroid cancer and tuberculosis.

DISCUSSION

This study showed that ^{18}F-FDG PET is a useful method to detect early recurrences in patients with cervical cancer who showed no evidence of disease after treatment. Because all patients in the study showed no evidence of disease on physical examination, tumor markers, chest radiography, and annual pelvic CT or MRI, the 28 patients who were confirmed to have recurrence were detected only by ^{18}F-FDG PET.

It is estimated that approximately 35% of patients with invasive cervical cancer will have recurrent or persistent disease after therapy (2). Conventional imaging modalities such as CT or MRI were performed to detect early recurrent lesions; however, the detection rate is low (18). Sugawara et al. (10) reported that ^{18}F-FDG PET could detect lymph node metastasis more accurately than CT or MRI in patients with cervical cancer. ^{18}F-FDG PET could detect recurrences in small lesions of <1 cm and in the retrovesical area, which are frequently obscured by postradiation fibrosis. In a retrospective study performed on 13 patients with cervical cancer, ^{18}F-FDG PET could detect recurrences in 10 patients who had recurrences in the iliac lymph node, liver, lung, and paraaortic lymph node, suggesting a promising role of ^{18}F-FDG PET in cervical cancer (16).

The higher feasibility of ^{18}F-FDG PET over CT or MRI in detecting recurrences of cervical cancer may be explained by several factors. First, because ^{18}F-FDG PET scans can provide functional information on the lesions rather than anatomic images, it can detect recurrent lesions independent of the size (7–9). Furthermore, as already well recognized in head and neck cancers (6,19), ^{18}F-FDG PET provides more important images when anatomy has been distorted after surgery or radiation treatment. In our study, ^{18}F-FDG PET could detect occult recurrent metastasis in lesions such as the vaginal cuff, retrovesical area, and pelvic sidewall, where it is difficult to differentiate between fibrosis and recurrence.

The other advantage of ^{18}F-FDG PET is that it can show a whole-body image at one time. Approximately 70% of recurrences of cervical cancer are estimated to be distant or a combination of local and distant metastases (2). Most of the distant metastasis is detected in an already far-advanced state with clinical symptoms such as cough, hemoptysis, and pain. Because ^{18}F-FDG PET can provide a whole-body image at one time, distant metastases, which are usually not evident on routine pelvic CT or MRI, can easily be detected by ^{18}F-FDG PET. In this study, ^{18}F-FDG PET was useful in detecting metastasis in lesions such as the scarlene lymph node, lung, and mediastinum, where it was difficult to detect recurrence with conventional imaging modalities. Two cases each of pulmonary tuberculosis and thyroid cancer, incidentally detected in this study, also benefited from the whole-body image of ^{18}F-FDG PET.

Most recurrence in cervical cancer is known to occur within 2 y after therapy (2); however, the peak period of

TABLE 2
Detection of Early Recurrence with ^{18}F-FDG PET in Cervical Cancer

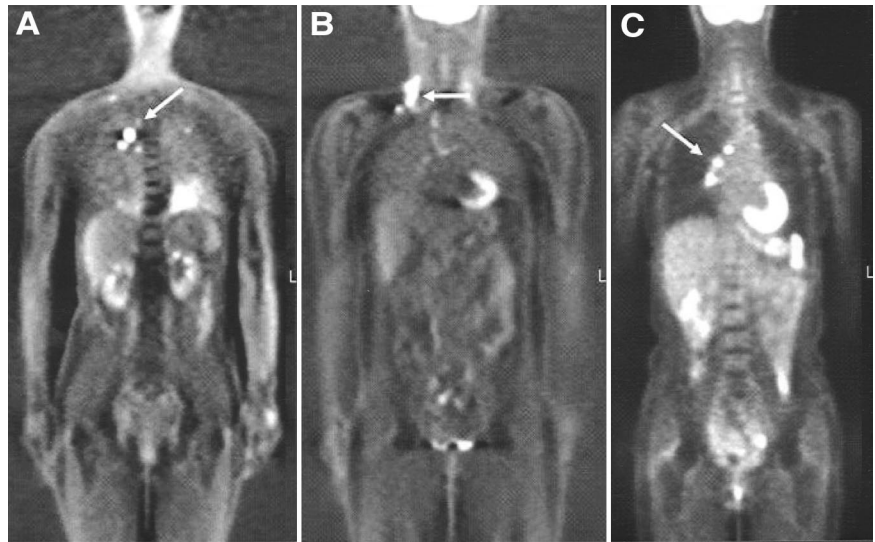| Parameter	No. of patients	%
No. of patients	249	
Negative PET scan	169	67.8
True-negative	166	66.6
False-negative	3	1.2
Positive PET scan	80	32.1
True-positive	28	11.2
False-positive	52	20.8

FIGURE 1. Detection of recurrences by ^{18}F-FDG PET in patients with cervical cancer showing no evidence of disease. (A) Multiple recurrences in lung (↙). (B) Right scalene lymph node metastasis (←). (C) False-positive hilar lymph nodes (↘).

recurrence detected by ^{18}F-FDG PET in this study was 9–12 mo after treatment. This finding suggested that ^{18}F-FDG PET might detect recurrences earlier than historical data with conventional methods (*2*). Moreover, because the recurrence rate of cervical cancer is higher and distant metastasis is more common in advanced diseases, ^{18}F-FDG PET is a more useful method to detect recurrence in patients with advanced stages of disease.

Our results showed that the false-positive rate of ^{18}F-FDG PET was relatively high in lesions such as the hilum, neck, lung, inguinal area, and axillae. Three false-negative cases were illustrated in the paraaortic lymph node and the retrovesical area. Even though we usually correct the standardized uptake value according to the depth of the lesions by the transmission scan, it was highly likely that there were more false-positive lesions in the superficial area than in deep areas such as the paraaortic lymph node and the

retrovesical area. More thoughtful consideration according to the depth of lesions may be necessary in interpreting the significance of ^{18}F-FDG uptake. However, the most important step for detection of early recurrences is a suspicion of recurrence, which leads the physician to investigate for any early recurrence, indicating that the clinical feasibility of ^{18}F-FDG PET is relatively high despite of the high false-positive rate. Although the positive predictive value is relatively low, the high negative predictive value of ^{18}F-FDG PET in this study suggests that the clinical feasibility of ^{18}F-FDG PET is a method to assure the patients who are anxious about a possible recurrence.

All patients in this study showed no evidence of disease on conventional methods after treatment and were monitored by the standard protocol. However, because all patients with no evidence of disease were not investigated by ^{18}F-FDG PET, we could not exclude completely a selection
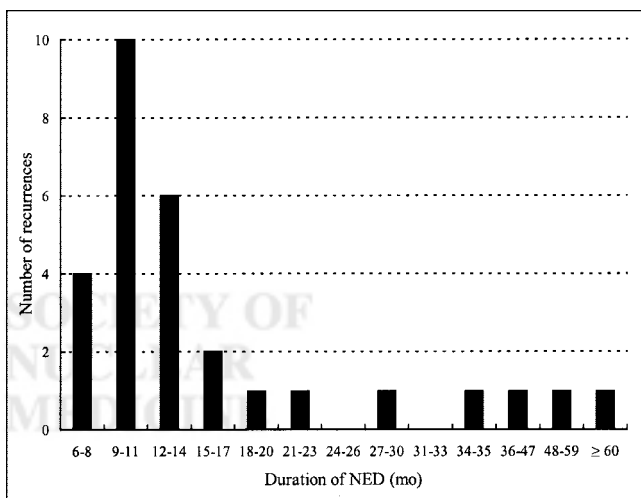

FIGURE 2. Detection of recurrences by ^{18}F-FDG PET in patients with cervical cancer showing no evidence of disease (NED).
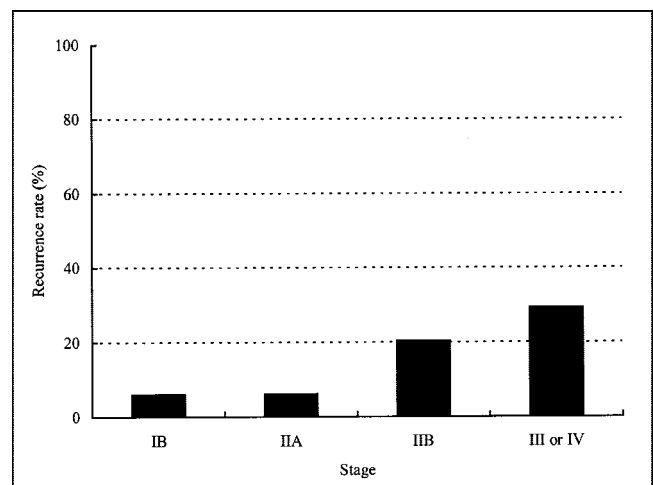

FIGURE 3. Detection of recurrences by ^{18}F-FDG PET according to stage of patients with cervical cancer showing no evidence of disease.

Location	No. of positive	No. of true-positive	No. of false-negative	Sensitivity (%)	Specificity (%)
Hilar	26	7	0	100	92
Scarlene lymph node	12	5	0	100	97.1
Lung	11*	6	1	85	97.9
Neck	9	0	0	—	96.4
Mediastinum	8	2	0	100	97.5
Iliac	7	5	0	100	99
Retrovesical	4	3	1	75	99.5
Inguinal	4	0	0	—	98.4
Paraaortic	3	3	1	75	100
Skull	2	0	0	—	99.2
Axillae	2	0	0	—	99
Colon	2	0	0	—	99
Liver	2	2	0	100	100
Spine	1	1	0	100	100
Chest wall	1	1	0	100	100

*Two cases of tuberculosis.

bias. Despite a possible selection bias, because the patient characteristics and recurrence rate did not differ significantly from the historical data, we believe that the selection bias may not be significant (*2*). A further prospective study is needed.

For further evaluation of the clinical feasibility, the cost-effectiveness of ^{18}F-FDG PET should be evaluated. The high negative predictive value in this study suggests that the indication for ^{18}F-FDG PET should be given thoughtful consideration after proper evaluation of the cost-effectiveness. Even though we did not elucidate the cost-effectiveness of ^{18}F-FDG PET, we suggest that evaluation for recurrence with ^{18}F-FDG PET is beneficial in patients with risk factors for recurrence. Further investigation is necessary for the proper indication and cost-effectiveness of ^{18}F-FDG PET in patients with cervical cancer.

CONCLUSION

In this study, we showed that ^{18}F-FDG PET was a useful method to detect early recurrence in cervical cancer; however, we did not evaluate the cost–benefit effect or, more importantly, the survival impact of ^{18}F-FDG PET on the treatment of cervical cancer. Nevertheless, we suggest that ^{18}F-FDG PET at least 1 y after treatment in advanced stages might be useful to detect early recurrence in patients with cervical cancer, even if they showed no evidence of disease after therapy.

FIGURE 4. ^{18}F-FDG PET incidentally detected 2 cases each of thyroid cancer and tuberculosis in patients with cervical cancer who showed no evidence of disease after treatment. (A) Thyroid cancer (←). (B) Tuberculosis (↙).

REFERENCES

1. Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1998. *CA Cancer J Clin.* 1998;48:6–29.
2. Disaia PJ, Creasman WT. *Clinical Gynecologic Oncology.* 6th ed. St. Louis, MO: Mosby; 2001:89–93.
3. Vinnicombe SJ, Norman AR, Nicolson V, et al. Normal pelvic lymph nodes: evaluation with CT after bipedal lymphangiography. *Radiology.* 1995;194:349–355.
4. Warburg O. On the origin of cancer cells. *Science.* 1956;123:309–314.
5. Wahl RL, Hutchins GD, Buchsbaum DJ, et al. ^{18}F-Fluoro-2-deoxy-D-glucose uptake into human tumor xenografts: feasibility studies for cancer imaging with positron-emission tomography. *Cancer.* 1991;67:1544–1550.
6. Anzai Y, Carroll WR, Quint DJ, et al. Recurrence of head and neck cancer after surgery or irradiation: prospective comparison of 2-deoxy-2-[F-18]fluoro-D-glucose PET and MR imaging diagnoses. *Radiology.* 1996;200:135–141.
7. Wahl RL, Quint LE, Greenough RL, et al. Staging of mediastinal non-small cell lung cancer with FDG PET, CT, and fusion images: preliminary prospective evaluation. *Radiology.* 1994;191:371–377.
8. Gritters LS, Francis IR, Zasadny KR, et al. Initial assessment of positron emission tomography using 2-fluorine-18-fluoro-2-deoxy-D-glucose in the imaging of malignant melanoma. *J Nucl Med.* 1993;34:1420–1427.
9. Avril N, Dose J, Janicke F, et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol.* 1996;14:1848–1857.
10. Sugawara Y, Eisbruch A, Kosuda S, et al. Evaluation of FDG PET in patients with cervical cancer. *J Nucl Med.* 1999;40:1125–1131.

11. Shimotsu Y, Ishida Y, Fukuchi K, et al. Fluorine-18-fluorodeoxyglucose PET identification of cardiac metastasis arising from uterine cervical carcinoma. *J Nucl Med*. 1998;39:2084–2087.

12. Rose PG, Adler LP, Rodriguez M, et al. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol*. 1999;17:41–45.

13. Umesaki N, Tanaka T, Miyama M, et al. Early diagnosis and evaluation of therapy in postoperative recurrent cervical cancers by positron emission tomography. *Oncol Rep*. 2000;7:53–56.

14. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol*. 2001;19:3745–3749.

15. Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology*. 2001;218:776–782.

16. Kerr IG, Manji MF, Powe J, et al. Positron emission tomography for the evaluation of metastases in patients with carcinoma of the cervix: a retrospective review. *Gynecol Oncol*. 2001;81:477–480.

17. Narayan K, Hicks RJ, Jobling T, et al. A comparison of MRI and PET scanning in surgically staged loco-regionally advanced cervical cancer: potential impact on treatment. *Int J Gynecol Cancer*. 2001;11:263–271.

18. Hricak H, Yu KK. Radiology in invasive cervical cancer. *AJR*. 1996;167:1101–1108.

19. Strasuss LG, Clorius JH, Schlag P, et al. Recurrence of colorectal tumors: PET evaluation. *Radiology*. 1989;170:329–332.