Usefulness of F-18 FDG PET/CT in Assessment of Recurrence of Cervical Cancer After Treatment

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Abstract

Objective Until now, serum tumor markers, physical examination, and conventional imaging modalities, such as CT or MRI, have been used in assessment of recurrence of cervical cancer after treatment. However, CT and MRI provide only anatomical data, which makes analysis of post-treatment change difficult. This study aims to explore the effectiveness of PET/CT, a new scanning device that combines PET and CT, in evaluation of cervical cancer lesions in patients with suspected recurrence.

Methods We studied 51 patients suspected of recurrence among those who underwent F-18 FDG PET/CT for cervical cancer follow-up at Gachon University Gil Hospital between June 2006 and August 2009. Patients were considered to be at risk for recurrence if they reported symptoms that were clinically suggestive of recurrence, or if physical examination showed abnormalities, serum tumor marker levels rose, or follow-up images revealed changes, such as new lesions or swelling of previous sites. Sensitivity, accuracy, specificity, and positive and negative predictive values of PET/CT were measured.

Results A total of 37 patients were confirmed with recurrence or metastasis, 13 of whom were diagnosed histologically. Measured across all patients, PET/CT scored 97.3% on sensitivity, 71.4% on specificity, a positive predictive value of 90%, a negative predictive value of 90.9%, and an accuracy of 90.2%. PET/CT yielded only one false negative diagnosis and four false positives.

Conclusion As F-18 FDG PET/CT has high sensitivity and negative predictive value in diagnosis of recurrent cervical cancers, it is expected that it will be useful for clinical determination of recurrence and prevention of unnecessary additional treatments. The hope is that a future study on a larger scale will contribute further to determination of the efficacy of PET/CT.

Keywords Cervical cancer · PET/CT · Recurrence

Introduction

Cervical cancer is one of the most common gynecological tumors and is a significant global public health concern, with approximately 81% of all cases occurring in developing countries [1]. Although introduction of diagnostic methods, such as the PAP smear, has increased the rate of early detection and treatment of tumors, thus improving the results of treatment, the rate of recurrence after appropriate treatment is around 30%. Hence, early detection and treatment of recurrences are very important for aiding the patient's recuperation in the long term [2, 3]. Patient symptoms, physical examination, tumor marker level, and morphological imaging methods, such as CT or MRI, are usually used for evaluation of recurrence; however, these conventional imaging modalities are limited in their ability

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Table 1 Patient characteristics

Characteristics	Values
Patients (<i>n</i>)	51
Age (years)	
Mean	53
Range	28–76
FIGO stage	
0	2
I	20
II	25
III	3
IV	1
Histopathology	
Squamous cell carcinoma	46
Mixed carcinoma	5
Treatment methods	
Surgery (including conization)	5
Surgery + radiotherapy	4
Surgery + chemoradiotherapy	19
Chemoradiotherapy	23
Reasons for PET/CT evaluation	
Symptoms suggestive of recurrence	16
Physical examinations revealed abnormalities	5
Increased serum tumor marker levels	21
Abnormal follow-up images	9

to accurately detect post-surgery or post-radiotherapy change, which include fibrosis, hemorrhage, and inflammation [4–6].

PET, which utilizes the glucose analogue known as F-18 FDG as a tracker for evaluation of tumor tissue metabolism, was introduced and is used for diagnosis, treatment, and follow-up in various kinds of tumor; however, it could not clearly distinguish between anatomical locations, and, therefore, suffered from low specificity despite its excellent sensitivity [7–11]. PET/CT, which combines PET and CT,

has recently been introduced, and has received much attention. Although a substantial number of previous studies have made conclusions about the use of PET, studies on the effectiveness of PET/CT remain relatively few. This study was aimed at exploration of the usefulness of F-18 FDG PET/CT for assessing suspected recurrences during follow-up in patients who have been treated for cervical cancer.

Subjects and Methods

Subjects

This study evaluated 51 patients suspected of developing recurrence who were selected on the basis of retrospective inspection of their medical records from among those who underwent F-18 FDG PET/CT at Gachon University Gil Hospital between June 2006 and August 2009. Cases considered to be at risk were those in which (1) the patient reported symptoms that were clinically suggestive of recurrence, such as abnormal vaginal bleeding, leg edema, pain in the thigh area, and oliguria, (2) physical examinations revealed abnormalities, (3) serum tumor marker levels (SCC, CEA) had risen (including cases with abnormal levels as well as cases in which the value was still within the normal limits but a gradual increase was noted), and (4) follow-up images revealed developments such as new lesions or changes at previous sites, including changes in size or morphology. Patients who refused the PET/CT for financial reasons or who had other malignancies were excluded from this study.

PET/CT Imaging

After fasting for 6 h, patients were intravenously injected with 10–15 mCi (370–555 MBq) of F-18 FDG 1 h prior to imaging. Blood sugar levels of all patients were

Fig. 1 A 41-year-old patient who received chemotherapy and radiotherapy for treatment of squamous cell carcinoma of the uterine cervix underwent PET/CT for evaluation of a palpable left axillary mass. PET/CT shows intense left axillary lymph node uptake (*arrow*), which was confirmed as metastasis by tissue biopsy

Table 2 Site of tumor recurrence

Site of recurrence	Number
Regional	5
Abdominal lymph node	6
Pelvic lymph node	10
Other lymph nodes (axillary, mediastinal, neck, supraclavicular)	7
Bone	2
Lung	5
Presacral soft tissue	1
Peritoneal seeding	1

measured prior to injection of F-18 FDG, and none showed results above 150 mg/dl. No contrast agent was administered orally or intravenously, and images were taken without insertion of urinary catheters. The PET/CT model used was Biograph6 (Siemens Medical Solutions, Germany). The CT image was first taken from the cranial base to the proximal femur, with the patient in a supine position, and then in the opposite direction, from the proximal femur to the cranial base. Emission scans were taken from each of six to eight beds for 2 min. Resulting images were reconstructed using the OSEM (ordered subsets expectation maximization) method. Attenuation equalization was achieved using CT.

Evaluation of Images and Diagnosis of Recurrence

PET/CT images were interpreted by two experienced nuclear medicine physicians without knowledge of any clinical data or images derived from use of other scanning tools. Cases showing areas with higher nonphysiological intakes than in adjacent tissues were judged to be positive. For analysis of conventional imaging modalities, including ultrasonography, CT, and MRI, the study referred to the interpretation of radiologists.

As for the diagnosis of recurrence, cases that were histologically diagnosed as affirmative, that displayed

further development of the condition, such as increase in the size or number of affected areas on imaging tests conducted as part of follow-up lasting 6 months or longer, or that reacted to post-radiochemotherapy treatment were confirmed as recurrences. Based on this patient-based data, sensitivity, specificity, positive and negative predictive values, and accuracy were measured.

Results

Of the 51 patients in this study, 46 were diagnosed with squamous cell carcinoma, with those at FIGO stage II being the largest group (Table 1).

A total of 37 patients were confirmed with recurrence or metastasis, and of those, 13 received a definite histological diagnosis, with the remaining 24 diagnosed through indicators that included continuously deteriorating lesions on follow-up images or further developments despite treatment or significant decreases in size due to treatment. The most common locations of recurrence were the pelvic and abdominal lymph nodes, with one case each of recurrence at the axillary (Fig. 1), supraclavicular, mediastinal, and cervical lymph nodes (Table 2).

Regarding the analysis of the causes that prompted F-18 FDG PET/CT, nine patients became subjects following findings of abnormally large abdominal and pelvic lymph nodes and pulmonary metastasis on conventional imaging modalities. All of these patients showed increased intakes on PET/CT and later received a positive diagnosis on histological/radiological tests. In one case, additional bone metastasis was discovered through PET/CT (Fig. 2). Among the 16 patients who were referred for PET/CT due to abnormal symptoms, lesions suspected of recurrence were revealed in six cases, three of them were confirmed by follow-up CT and the others were confirmed histologically. Five patients were referred for PET/CT due to suspicion of recurrence following physical examination. In all of these cases, PET/CT found suspect lesions that were all later diagnosed as recurrences, except for one. Also, in the case

Fig. 2 A 72-year-old patient who underwent surgery and received chemotherapy and radiotherapy for treatment of squamous cell carcinoma of the uterine cervix underwent PET/CT for evaluation of an abnormal mediastinal lymph node that was suspicious for metastasis. PET/CT shows increased mediastinal lymph node uptake, and, additionally, demonstrates bone metastasis in the sacral area (*thick arrow*)

Table 3 Recurrence and PET/CT findings according to the main reason for PET/CT evaluation

	Patients	PET/CT positive	True positive
Abnormal symptoms	16	7	6
Abnormal physical exam	5	5	4
Tumor marker elevation	21	19	18
Abnormal conventional imaging findings	9	9	9

of the 21 patients referred for PET/CT because of increases in serum tumor markers, PET/CT and tracking tests confirmed recurrence with all except two (Table 3).

When calculated for the entire patient group, PET/CT scored a sensitivity of 97.3%, a specificity of 71.4%, a positive predictive value of 90%, a negative predictive value of 90.9%, and an accuracy of 90.2%. False positives on PET/CT included a case in which PET/CT revealed increased uptake in the aortocaval region but despite no additional treatment, the serial follow-up scans on conventional imaging modalities found no abnormalities, and another case in which recurrence was suspected due to a lump felt inside the pelvis and increased intakes detected on PET/CT, which was shown to be an ovarian abscess (Fig. 3). The remaining two false positive cases included one insufficiency fracture and one case of pulmonary tuberculosis. There was a false negative result, which was finally diagnosed as periurethral metastasis (Table 4).

Discussion

Cervical cancer has the second highest incidence, after breast cancer, among malignant tumors in women worldwide and is most common among women 45–55 years of age. Histologically, squamous cell carcinoma constitutes

approximately 80–90% of cases, and adenocarcinoma makes up the remaining 10–20%. Adenosquamous carcinoma, which is a mixed carcinoma that combines the characteristics of both squamous cell carcinoma and adenocarcinoma, represents 2–5% of cases [12]. In Korea, cervical cancer constituted 6.7% of all malignant tumors in women, ranking sixth behind breast, thyroid, stomach, colon, and lung cancers; thus, it was shown to be a tumor that still occurs with relatively high incidence. However, its incidence has shown a downward trend, with a yearly rate of change of −5.2%, and a 5-year survival rate of 81.1%, which is the third highest after thyroid and breast cancer. Among causes of decreased incidence and increased survival rate, early detection and treatment due to factors such as improvement in hygiene and campaigns promoting regular checkups have been significant. However, in order to aid the patient's recuperation in the long term, early detection of post-treatment recurrence and its appropriate treatment is just as important.

Recurrence can be determined in several ways during the follow-up period, and images, usually using CT or MRI, are taken on a regular basis [2]. However, it is difficult to make assessments using these methods when there are structural changes resulting from surgery or radiotherapy, and the images are also limited by the fact that they can only discern changes in size [13–15]. In contrast with conventional anatomical imaging modalities, such as CT, MRI, and ultrasonography, F-18 FDG PET takes advantage of the fact that tumor cells have higher sugar metabolic rates than normal cells to acquire images and provide functional data, and, thus, has been employed widely as a complementary diagnostic tool with conventional imaging modalities. With the advent of PET/CT, which combines PET and CT, simultaneous acquisition of both functional and anatomical data on tumors is now possible [16]. In a previous study by Ryu et al. with a relatively large pool of 249 patients, F-18 FDG PET was used to assess recurrence after treatment for cervical cancer and scored a sensitivity of 90%, a

Fig. 3 A 35-year-old patient diagnosed with FIGO stage IA uterine cervical cancer, who had had radical trachelectomy, underwent PET/CT for evaluation of consistent abdominal pain. PET/CT shows increased uptake in the right pelvic cavity (*arrow*), which was suspicious for recurrence, but was finally diagnosed as an ovarian abscess by contrast-enhanced CT (*thick arrow*) and clinical follow-up

Table 4 Patient-based diagnostic accuracy of PET/CT

	True positive (<i>n</i>)	True negative (<i>n</i>)	False positive (<i>n</i>)	False negative (<i>n</i>)
PET/CT	36	10	4	1
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PET/CT	97.3	71.4	90.0	90.9

specificity of 76%, and an accuracy of 74% [17]. In other studies, sensitivities between 86 and 100%, specificities between 60 and 94%, and accuracies between 70 and 97% were reported [18–22]. As for the efficacy of PET/CT, the study by Chung et al. reported a sensitivity of 90.3%, a specificity of 81%, and an accuracy of 86.5% [23], and in the study by Kitajima et al., PET/CT scored a sensitivity of 92%, a specificity of 93%, and an accuracy of 92% [24]. PET/CT also performed well in the present study, with a sensitivity of 97.3%, a specificity of 71.4%, a positive predictive value of 90%, a negative predictive value of 90.9%, and an accuracy of 90.2%. In particular, it scored highly on sensitivity and accuracy, and its effective use for clinical determination of recurrence and prevention of unnecessary additional treatments is expected.

Of the 37 patients diagnosed with recurrence in this study, recurrence occurred outside the pelvis in 12 cases. PET/CT has an advantage over standard abdominal CT and pelvic MRI in assessment of lesions that occur outside the pelvis because it covers a large area from the cranial base to the proximal femur. Moreover, because the PET/CT provides metabolic and anatomic information at the same time, it can detect abnormalities when the lesion is distorted by previous surgery or radiation therapy better than PET or CT alone. Furthermore, although PET/CT's spatial resolution of 4–5 mm has been considered a drawback for its ability to detect smaller local recurrences [25–27], PET/CT found five cases of local recurrence in this study. The largest one was 3.2×3.8 cm and the smallest case was 1.2×1.5 cm. On the other hand, one of the problems of both PET and PET/CT is that distinguishing between inflammatory lesions and tumors can be difficult, as they both have increased intakes. Also, in this study, PET/CT falsely identified four cases as positive: an abdominal lymph node enlarged from inflammation, an ovarian abscess, a pulmonary tuberculosis, and an insufficiency fracture of pelvic bone. These errors lowered the specificity and the positive predictive value. In the case involving an ovarian abscess, it is believed that had contrasting agent been used with PET/CT, the images could have better portrayed the lesion's form and characteristics, which would have contributed to specificity and accuracy [28]. In this study, the number of patients referred for PET/CT under suspicion of recurrence was small, and only 13 cases were confirmed histologically with recurrence; these might be regarded as limitations.

In conclusion, in assessment of patients suspected of developing recurrence after treatment, F-18 FDG PET/CT provides both anatomical and functional data, aiding accurate restaging, and enhancing the patient's recuperation. The hope is that a study conducted on a larger scale, involving a larger group of patients, will further contribute to determining the efficacy of PET/CT in the future.

Conflict of Interest We declare that the authors have no conflict of interest.

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