Clinical Research

Application of $^{18}$F-FDG PET/CT in cervical cancer with elevated levels of serum squamous cell carcinoma antigen during the follow-up

Ying-Ying Hu, Xin-Ru Sun, Xiao-Ping Lin, Pei-Yan Liang, Xu Zhang and Wei Fan

Abstract] Background and Objective: Accurate and early diagnosis of recurrence for cervical cancer after the treatment and aggressive salvage treatment could improve the prognosis of this disease. Serum squamous cell carcinoma antigen (SCCAg) is the most commonly used tumor marker for the detection of asymptomatic recurrence of cervical cancer. This study was to evaluate the application and value of $^{18}$F-FDG PET/CT in cervical cancer with elevated of serum SCCAg level during the follow-up. Methods: Thirty-one patients with cervical cancer with elevated serum SCCAg level during the follow-up undergoing $^{18}$F-FDG PET/CT in Sun Yat-sen University Cancer Center between August 2005 and November 2008 were entered into this retrospective study. The pathological types, the serum SCCAg level, PET/CT results, results of other imaging modalities, pathological and clinical follow-ups were recorded. Results: All 31 patients’ pathological examination showed squamous cell carcinoma, including three adenosquamous carcinoma. Lesions of all patients were examined by PET/CT. Three patients had local recurrence in the uterus or vagina. 28 had metastatic disease. Of these 31 patients, three were confirmed to have local recurrent disease, 27 were verified to have metastatic disease and one was diagnosed as primary lung squamous cell carcinoma by pathological or clinical manifestations. The total detection rate of PET/CT for malignancy was 100\% (31/31); the diagnostic accuracy of PET/CT for recurrent cervical cancer was 96.8\% (30/31). The levels of serum SCCAg during the follow-up were 1.5--37.8 ng/ml. There was no relation between the level of serum SCCAg and the maximum standard uptake value (SUVmax) of PET/CT. Compared with other imaging modalities, PET/CT was more efficient in detecting recurrence and finding more lesions. Conclusions: An elevated level of SCCAg in cervical cancer during the follow-up indicates tumor recurrence. PET/CT is efficient in detecting the recurrence and has high diagnostic accuracy.

Key words: cervix cancer, squamous cell carcinoma antigen, tumor recurrence, $^{18}$F-FDG, PET/CT

Serum squamous cell carcinoma antigen (SCCAg) is the most commonly used tumor marker for detection and follow-up of cervical cancers. Elevation of the serum SCCAg level during the follow-up of cervical cancer patients indicates tumor recurrence. However, not all suspected recurrent cervical cancer patients with
an elevated level of serum SCCAg during the follow-up were detected lesions in physical examination and by traditional imaging tests. Study by Micke et al. found that 71% of patients with recurrent cervical cancer first showed an elevated level of serum SCCAg, and the time from the increase in serum SCCAg to detection of tumor lesions in clinic was 1-16 months, with a medium period of 3.1 months for the early detection of the tumor. In a study by Ma et al., an elevated level of serum SCCAg was detected in 61 patients with cervical cancer patients during the follow-up, 20 of which had no positive clinical and imaging findings. 18F-FDG PET/CT can provide information on both the proliferation and metabolism of tumor cells in the body and on the anatomical structure of the tumor lesions, thereby enhance the efficiency of detecting the lesions. In addition, PET/CT imaging has the advantage of whole body metastases screening in a single scan, useful in the systemic detection of tumor recurrence. This study explored the application of 18F-FDG PET/CT in patients with elevated serum SCCAg during the follow-up, in order to assess the value of elevated SCCAg levels in cervical cancer during the follow-up.

**Data and Methods**

**Patient information.** Study subjects were chosen from patients with cervical cancer receiving PET/CT scan during the follow-up in our department between August 2005 and November 2008. Patients were enrolled according to the following criteria: the level of serum SCCAg (detected by fluorescence polarization immunoassay) changed from negative (<1.5 pg/L) to ≥ 1.5 pg/L; with the history of negative SCCAg ≥ 3 months; time from SCCAg detection to PET/CT imaging <3 weeks without any kind of treatments; with complete pathological and clinical follow-up information after PET/CT imaging, and those received clinical follow-up should have a follow-up time longer than six months. A total of 31 patients between 28 to 68 years old were selected, with a median age of 48 years. Complete history and information of patients were retrieved for retrospective analysis. The pathological type, clinical staging, treatments, pre-treatment SCCAg level, period of negative SCCAg during the follow-up, the increased level of SCCAg during the follow-up, PET/CT imaging results, results of other imaging modalities and pathological and clinical follow-up information of the patients were recorded.

Among 31 patients, there were three cases of squamous carcinoma, one case of severe dysplasia/carcinoma in situ, 11 cases of poorly differentiated squamous cell carcinoma, one case of poorly differentiated squamous cell carcinoma with adenoid differentiation, two cases of poorly/moderately differentiated squamous cell carcinoma, 10 cases of moderately differentiated carcinoma and three cases of well differentiated and moderately/well differentiated squamous cell carcinoma. According to the 1995 diagnostic criteria by International Federation of Gynecology and Obstetrics (FIGO), there were one case of carcinoma in situ, eight cases of stage IB, seven cases of stage IIA, eight cases of stage IIB, two cases of stage IIIA and five cases of stage IIIB. Fourteen cases received surgery plus chemotherapy and radiotherapy, four cases underwent surgery plus radiotherapy, three cases received surgery plus chemotherapy, seven cases underwent chemotherapy plus radiotherapy and three cases received radiotherapy alone. Among 31 patients, the SCCAg levels before the initial treatment were ≥ 1.5 pg/L in 15 cases and <1.5 pg/L in six cases; the other 10 patients did not receive SCCAg test before the treatment. All 31 patients had the history of negative SCCAg during or after the treatment, and the period of negative SCCAg was 3-31 months (median, 10 months). Before PET/CT imaging, the levels of SCCAg of the patients were 1.5 pg/L - 37.8 pg/L, of which there were 17 cases of 1.5 pg/L - 5 pg/L, six cases of 5 pg/L - 10 pg/L, five cases of 10 pg/L - 30 pg/L and three cases of ≥ 30 pg/L.

**Imaging method of 18F-FDG PET/CT.** Patients were required to fast for more than 6 h, and routine blood glucose level was measured before the test. Blood glucose of the subjects
should be below 8.1 mmolL⁻¹ and subcutaneous insulin was injected when necessary. ¹⁸F-FDG (4.4-7.4 MBq/kg) was intravenously injected. ¹²⁴F-FDG was produced by Beijing Atom Hi-Tech Guangzhou branch, radiochemical purity > 90%. Patients were allowed to lay down in a quiet dark room to rest for 45-60min. PET/CT imaging was performed after emptying the bladder. The PET/CT imaging apparatus used was Discovery ST 16 produced by GE company. Patients were on a supine position and the scanning range was from the top of cranium to middle of femur. CT scan was performed by the automatic milliamper tracking method, using the tube voltage of 140Kv. CT reconstruction was performed using the standard reconstruction method, with the exception of lung for which the lung window reconstruction method was used. PET acquired 5-7 beds in the 2D mode, 2.5min/bed. CT images were used for decay correction of PET images, and the OSEM iteration method was applied for PET reconstruction using the slice thickness of 3.75mm. Reconstructed PET images and CT images were merged to obtain PET/CT fusion images using the fusion software provided in the system. The standard uptake value (SUV) was automatically calculated based on the body weight of the patients, injected dose and half life.

**PET/CT diagnosis and image analysis.** Distribution of ¹⁸F-FDG in PET images matched the physiological characteristics of glucose metabolism and ¹⁸F-FDG excretion. Qualified PET/CT images were judged by the good match of the fused image. Images were analyzed by two nuclear medicine physicians with rich experiences in PET/CT diagnosis, referring to detailed history before diagnosis.

Malignant diagnosis of the lesion was based on abnormal morphology on PET/CT and higher FDG uptake by the lesion than mediastinal blood pool. SUV of all lesions in each patient was determined by outlining regions of interest, and the highest SUV value among all regions of interest was recorded as the SUVmax.

**Statistical analysis.** SPSS 11.0 statistical software was applied to draw scatter plot of serum SCCAg and PET/CT SUVmax. Pearson correlation analysis was used to analyze the correlation between SCCAg and SUVmax, and the resulting correlation coefficient was subjected to statistical tests.

**Results**

**PET/CT imaging results.** The lesions of all 31 cervical cancer patients with elevated SCCAg during the follow-up were detected by PET/CT. Three cases of local recurrence at uterus or vagina and 28 cases of metastases, including five cases of single metastasis and 23 cases of multiple metastases, were identified.

According to the anatomical zoning standard, which divided the human body into head and neck, chest, abdomen and pelvis/perineum, the anatomical distributions of the lesions in all 31 patients were as follows: lesions of 14 patients were located in a single anatomical site, including seven cases at pelvic and perineal areas, two cases at the abdominal area, four cases at chest and one case at neck. The remaining 17 cases had lesions at multiple sites, including six cases at pelvic cavity + abdominal area, two cases at pelvic cavity + abdominal area + chest area, three cases at pelvic + abdominal + neck area, two cases at abdominal + chest + neck areas, one case at abdomen + neck and one case at chest + neck. Multiple lesions across the whole body with bone metastases were seen in two cases, and all lesions at neck had supraclavicular lymph node metastasis. Among all lesions in 31 patients, the most common metastasis was lymph node metastasis, detected in 26 patients, followed by four cases of lung metastasis, two cases of bone metastasis, and two cases of liver metastasis and portal vein tumor thrombus.

**Serum SCCAg level and PET/CT results.** Among 17 patients with the SCCAg level of 1.5 pg/L-5 pg/L, one case had local recurrence at vagina, and there cases had metastasis at a single site and 13 cases had metastasis at multiple sites. Among six patients with 5 pg/L ≤ SCCAg <10 pg/L, there was one case with metastasis at a single site and five cases at multiple sites. In the five patients with 10 pg/L ≤ SCCAg <30 pg/L, there was one case of metastasis at a single site and four cases at multiple sites. In the three cases with SCCAg ≥ 30 pg/L, two patients had local...
recurrence at uterus and vagina, and one patient had multiple metastases.

Pathological and clinical follow-up results. Pathological examination through biopsy or after resection on at least one of the lesions detected by PET/CT was performed in 14 patients. Results showed 11 cases of lymph node metastasis and two cases of local recurrence at vagina. The rest one patient showed single metastasis at lung by PET/CT, and pathology after resection showed moderately/well differentiated primary squamous lung cancer. Seventeen patients were confirmed as recurrence (follow-up time> six months) by clinical follow-up (including follow-up by other imaging modalities), among which the SCCAg level of one patient returned to the normal level after chemotherapy and traditional Chinese medicine treatment, and the patient remained in stable condition during the follow-up. In another four patients, CT follow-up showed enlarged lesions and progressed disease after radiotherapy/chemotherapy. Four patients with the same or increased level of SCCAg after chemotherapy were clinically diagnosed as persistent cervical cancer recurrence after treatment. Among them three died during the follow-up and one case had reduced SCCAg after chemotherapy which was still above the normal level. This patient also died during the follow-up. Seven other patients, who gave up treatment, all died at the time of follow-up. The overall detection rate of PET/CT for malignancy was 100% (31/31), and the diagnostic accuracy for cervical cancer recurrence was 96.8% (30/31).

Comparison of PET/CT with other imaging modalities. Sixteen patients received other imaging tests before PET/CT imaging, including pelvic ultrasound for one case, abdominal ultrasound for one case, pelvic CT for two cases, pelvic MR for four cases, pelvic + abdominal CT for five cases, abdominal CT for one case, chest CT for three cases, of which one patient was subjected to both abdominal ultrasound and pelvic MR. Normal findings were reported in nine cases while lesions were detected in seven cases. Among the seven patients, two cases had local recurrence of a single lesion at uterus/vagina detected by both pelvic MR and PET/CT. The other five patients with multiple metastases were subjected to local imaging examinations, including pelvic MR for one case, pelvic CT for one case, pelvic + abdominal CT for one case and chest CT for two cases. Since the lesions located at multiple sites were across the body, PET/CT detected more lesions than local imaging methods. Comparisons of PET/CT imaging with other imaging modalities in these 16 patients are shown in Table 1. Pelvic metastases diagnosed by PET/CT in a 35 year-old woman with poorly-differentiated cervical squamous cell carcinoma, whose pelvic + abdominal CT had no abnormal findings with elevated SCCAg during the follow-up, is shown in Fig.1.

Statistical correlation analysis of serum SCCAg and PET/CT SUVmax. The correlation coefficient between the level of serum SCCAg and PET/CT SUVmax was r = 0.349, p=0.055>0.05, without statistical correlation. The scatter plot of SCCAg and SUVmax is shown in Fig.2.

Discussion

Serum SCCAg level after treatment is an independent factor to assess the treatment efficacy and evaluate prognosis of cervical cancer. An increase in the SCCAg level during the follow-up suggests tumor recurrence. Although the prognosis of cervical cancer patients could be improved by early, accurate diagnosis of recurrence and aggressive salvage treatment, early detection of the lesion in cervical cancer patients with elevated serum SCCAg in follow-up is still a clinical challenge. This study retrospectively analyzed 31 cases of cervical cancer patients who had an increased level of serum SCCAg of ≥ 1.5 pg/L from negative during the follow-up and received PET/CT imaging at the same time. Our results showed that the pathological types of all 31 patients were primary squamous cell carcinoma (including three cases of squamous carcinoma), consistent with the fact that SCCAg is a antigen for squamous cell carcinoma. Lesions
Table 1  Findings of PET/CT images and other imaging modalities for 16 cervical cancer patients during the follow-up

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>PET/CT findings (lesions)</th>
<th>Other imaging modalities</th>
<th>Findings (lesions) by other imaging modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paraortic LN and pelvic LN</td>
<td>Pelvic MR;</td>
<td>pelvic LN</td>
</tr>
<tr>
<td>2</td>
<td>Paraortic LN and pelvic LN</td>
<td>Pelvic CT;</td>
<td>pelvic LN</td>
</tr>
<tr>
<td>3</td>
<td>Neck LN, paraortic LN and pelvic LN, bone and bilateral lung</td>
<td>Chest CT;</td>
<td>bilateral lung</td>
</tr>
<tr>
<td>4</td>
<td>Paraortic LN and pelvic LN</td>
<td>Pelvic ultrasound;</td>
<td>negative</td>
</tr>
<tr>
<td>5</td>
<td>Paraortic LN and pelvic LN</td>
<td>Abdominal and pelvic CT;</td>
<td>negative</td>
</tr>
<tr>
<td>6</td>
<td>Neck LN, mediastinal LN, paraortic LN, pelvic LN and inguinal LN, psoas major and bone</td>
<td>Abdominal and pelvic CT;</td>
<td>pelvis LN</td>
</tr>
<tr>
<td>7</td>
<td>Neck LN, paraortic LN, pelvic LN</td>
<td>Abdominal and pelvic CT;</td>
<td>negative</td>
</tr>
<tr>
<td>8</td>
<td>Right lung hilar LN</td>
<td>Chest CT;</td>
<td>negative</td>
</tr>
<tr>
<td>9</td>
<td>Right lung hilar LN and mediastinal LN</td>
<td>Pelvic MR and abdominal ultrasound;</td>
<td>negative</td>
</tr>
<tr>
<td>10</td>
<td>Uterine body</td>
<td>Pelvic MR;</td>
<td>uterine body</td>
</tr>
<tr>
<td>11</td>
<td>Neck LN, mediastinal LN and bilateral lung hilar LN, bilateral lung</td>
<td>Chest CT;</td>
<td>bilateral lung</td>
</tr>
<tr>
<td>12</td>
<td>Vagina</td>
<td>Pelvic MR;</td>
<td>vagina</td>
</tr>
<tr>
<td>13</td>
<td>Neck LN, paraortic LN, pelvic LN</td>
<td>Abdominal and pelvic CT;</td>
<td>negative</td>
</tr>
<tr>
<td>14</td>
<td>Mediastinal LN, paraortic LN, pelvic LN and inguinal LN, left lung</td>
<td>Abdominal CT;</td>
<td>negative</td>
</tr>
<tr>
<td>15</td>
<td>Paraortic LN, pelvic LN</td>
<td>Pelvic CT;</td>
<td>negative</td>
</tr>
<tr>
<td>16</td>
<td>Pelvic cavity</td>
<td>Abdominal and pelvic CT;</td>
<td>negative</td>
</tr>
</tbody>
</table>

Note: LN, lymph node.

were detected in all 31 cases by PET/CT, which were mainly multiple metastases and distant metastases. There was no apparent association between the SCCAg value and characteristics of the lesion, and the SCCAg value was not statistically correlated with PET/CT SUVmax. Thirty-one patients were finally confirmed by pathological or clinical examinations as three cases of local recurrence at uterus and vagina, 27 cases of metastases and one case of primary lung squamous cell carcinoma. The detection rate of PET/CT for malignancy was 100% (31/31), and the diagnostic accuracy for cervical cancer recurrence was 96.8% (30/31).

Among the 31 patients in our study, 16 cases received other imaging examinations before PET/CT, showing no abnormal findings in nine cases. This could be explained by the location of lesions detected on PET/CT, i.e., among the 31 patients, only seven cases had lesions limited to pelvic cavity, while most patients had multi-site or distant metastases, thus local imaging tests were very likely to miss the lesions. We also noticed that although six patients had normal findings in abdominal (pelvic) CT tests, some of metastases detected by PET/CT were located at abdominal (pelvic) regions. We believe that the reason for diverged diagnosis of CT and PET/CT is as the following: CT may miss relatively small malignant lesions and those below the diagnostic threshold of CT; some metastases at abdomen and pelvic cavity do not have clear boundary with intestines and are mistaken as part of intestines, as shown in Fig. 1. These above reasons could also explain why in previous studies, metastases could not be found even with an elevated level of SCCAg during the follow-up of cervical cancer. This suggests that increase SCCAg during cervical cancer follow-up indicates tumor recurrence, but metastases could be at multiple or distant sites. In those patients, negative findings in routine imaging modalities cannot rule out the existence of metastasis, and PET/CT may improve the efficiency for detecting lesions. In this study, seven cases were detected of lesions by other imaging modalities, but PET/CT found more lesions in five of them, which shows the value of a single PET/CT imaging in comprehensive screening of tumor recurrence.
Figure 1  Pelvic metastases in a 35-year old woman with poorly–moderately differentiated squamous cervical cancer with elevated SCCAg during the follow-up detected by PET/CT

A: Transverse PET image shows intense uptake of FDG; B: Transverse fused PET/CT image shows intense FDG uptake in the lump of left pelvic cavity, which is close to the descending colon. D: Transverse PET image shows intense uptake of FDG; E: Transverse fused PET/CT image shows intense FDG uptake in the nodes of right pelvic cavity, which was confirmed at subsequent biopsy guided by ultrasound to be moderately differentiated squamous cancer; C and F: Abdominal and pelvic CT images of the metastatic lesions detected by PET/CT.

In 18F-FDG PET/CT imaging, SUV of the tumor lesion reflects proliferative activity of tumor cells. Other studies also showed that, relatively higher SUVmax of the lesion in PET imaging before treatment was correlated with the risk of lymph node metastasis. Therefore, SUVmax is considered as an independent indicator for prognosis. In addition, SCCAg level also correlates with tumor burden and proliferative activity of tumor cells. Our study firstly explored the correlation between SUVmax and SCCAg levels, and the result showed no statistical correlation between these two. Kato et al. also studied the correlation among SUV, SCCAg and CEA in 18F-FDG PET imaging of esophageal squamous cell carcinoma patients. Their results showed that SUV was not statistically correlated with relevant tumor markers, consistent with our results. It is possible that the level of serum SCCAg is an overall evaluation parameter for tumor burden of the body. Although SUVmax is also an indicator of
tumor burden, it prefers to reflect the glucose metabolism level of tumor cells in a single lesion, and the enzyme content of tumor cells or the size of tumor lesions can both affect SUVmax.

Chang et al. performed 18F-FDG PET imaging in 27 cases of cervical cancer patients with an increase in SCCAg during the follow-up (≥ 2.0 pg/L). Lesions were detected in 19 patients by PET, including two cases of severe pneumonia that was misdiagnosed by PET as mediastinal lymph node metastasis. It is noticeable that in the study by Chang et al., seven out of eight patients with negative PET findings showed SCCAg decline in follow-up and no recurrence and metastases were detected during the entire follow-up. The authors believe that a transient increase in SCCAg is caused by benign lesions, such as the confirmed three cases of benign skin lesions, one case of renal dysfunction and one case of pulmonary fibrosis. No pattern was detected in SCCAg values provided by the authors and they did not discuss the relevance of SCCAg levels in these seven cases of benign lesions. Although some benign lesions, such as renal failure, pulmonary disease, skin eczema, psoriasis and so on, did lead to an increase in SCCAg, the high rate (7/27) of a temporary increase in SCCAg in patients with cervical cancer during follow-up caused by benign lesions was not observed in our study. We can not rule out the random factors in case selection, so further studies including more cases are still in need.

In summary, the increased serum SCCAg level during follow-up of post-treatment cervical cancer indicates tumor recurrence, and PET/CT can effectively detect lesions with a high accuracy.


