Clinical Value of Combining $^{18}$F-FDG PET/CT and Routine Serum Tumor Markers in The Early Detection of Recurrence Among Follow-up Patients Treated for Cervical Squamous Cell Carcinoma

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Abstract

Objective: The purpose of this retrospective study was to investigate the role of $^{18}$F-Fluorodeoxyglucose Positron Emission Tomography ($^{18}$F-FDG PET/CT) and evaluate if combined elevated serum tumor markers levels improve the accuracy of $^{18}$F-FDG PET/CT in detecting recurrence of cervical squamous cell carcinoma.

Methods: A total number of 42 patients who were treated for cervical squamous cell carcinoma and had underwent $^{18}$F-FDG PET/CT for suspected recurrence of cervical cancer were retrospectively reviewed in this study and their clinical, pathological and serological data were collected and analyzed. The clinical value of combining $^{18}$F-FDG PET/CT with serum tumor markers was investigated.

Results: Among the 42 patients, $^{18}$F-FDG PET/CT was true positive in 25 (59.5%), false positive in 5 (11.9%), true negative in 12 (28.5%) and false negative in none. The overall patient-based sensitivity, specificity, accuracy, positive predictive value and negative predictive value of $^{18}$F-FDG PET/CT in detecting cervical recurrence were 100%, 70.6, 88.1%, 83.3%, and 100%, respectively. The accuracy of $^{18}$F-FDG PET/CT with combined squamous cell carcinoma antigen (SCC Ag) and carcinoembryonic antigen (CEA) elevation was 100% compared to only SCC Ag elevation and only CEA elevation, 90% and 33.3%, respectively. The positive predictive value of a positive $^{18}$F-FDG PET/CT with combined SCC Ag and CEA elevation was 100% for detection of recurrent cervical cancer. Also, the negative predictive value of a negative $^{18}$F-FDG PET/CT combined with normal SCC Ag and CEA levels was 100%.

Conclusion: $^{18}$F-FDG PET/CT is highly sensitive in the diagnosis of recurrent cervical cancer. When $^{18}$F-FDG PET/CT is associated with both SCC Ag and CEA elevation or only SCC Ag elevation, the accuracy is increased but not when associated with only CEA elevation. Positive $^{18}$F-FDG PET/CT associated with both tumor markers elevation can precisely predict recurrence. Moreover, normal levels of both tumor markers with a negative $^{18}$F-FDG PET/CT result may clinically reassure that a recurrence is absent.

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

Introduction

Cervical cancer figures among the second most frequently diagnosed malignancy of the female genital tract and is the third leading cause of cancer-related death among females in developing
countries [1]. In China, cervical cancer ranks sixth among the most commonly diagnosed female malignancy and is the eighth cause of cancer-related death among females [2]. The wide application of cytological screening for cervical cancer has reduced the incidence significantly in developed countries, but in developing countries, its incidence is still high [3, 4]. Cervical cancer is clinically staged by International Federation of Gynecology and Obstetrics system which has been revised in 2009 [5]. The current approach after diagnosis of cervical cancer is treatment guided by the clinical staging followed by tumor surveillance program with the aim for early recognition of recurrence [5, 6]. Although there have been great advances in the treatment of cervical cancer, detection of disease recurrence is still high during follow-up. About one-third of patients treated for cervical cancer develop recurrence within the first 2 years of completed therapy, ranging from 10-20% for stage IB1/IIA, up to 72% for stage IVA [7, 8]. The conventional follow-up procedures consist of systematic visits for patient history, complete physical examination, cytological investigations, tumor markers and imaging such as Computed Tomography and/or Magnetic Resonance Imaging. However, neither this methodology nor the tumor markers evaluated are part of a standardized protocol [9, 10]. Rising levels of tumor markers during follow-up can precede clinical detection of tumor recurrence [10]. Currently, Squamous cell carcinoma antigen (SCC Ag) and carcinoembryonic antigen (CEA) are the two serum tumor markers of choice by physicians for detection of recurrent cervical cancer. Raised levels of SCC Ag and CEA during follow-up of treated cervical cancer is observed in 62.5-92% and 29-64% of cases, respectively [11]. Although these tumor markers can predict recurrence before the lesions become clinically apparent, they cannot define the location of these lesions.

A review of the literature supports 18F-Fluorodeoxyglucose Positron Emission Tomography (18FDG PET) or 18F-Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography (18FDG PET/CT) as a promising tool for determination of metabolically active lesions during follow-up after therapy of various malignancies. These methods have the capacity to detect recurrent cervical cancer lesions, through pathologically increased tissue metabolism, which precedes the appearance of morphological changes detected by conventional imaging techniques [12, 13]. An intervention on 18FDG PET/CT using metabolic tumor parameter has been suggested to improve the diagnostic accuracy in several cancers. To date, semi-quantitative analysis is based on volume-of-interest 18FDG uptake where maximum standardized uptake value (SUVmax) is the backbone [14]. Previous reports have shown the clinical value 18FDG PET/CT in patients with elevated serum tumor markers during follow-up of cervical cancer. All these studies have evaluated the clinical significance of 18FDG PET/CT with elevated SCC Ag or CEA in the detection of cervical cancer recurrence, but currently, there are no reports on 18FDG PET/CT and combined elevation of SCC Ag and CEA for early recognition of recurrence in treated cervical cancer cases [15-18].

In this study, we evaluated the clinical value of combining 18F-FDG PET/CT and routine serum tumor markers in the early detection of recurrence among follow-up patients treated for cervical squamous cell carcinoma.

Materials and methods

Patients

We enrolled patients who underwent 18F-FDG PET/CT scan for detection of cervical cancer recurrence from February 2014 to June 2017 in our hospital, and their medical records were retrospectively reviewed. The inclusion criteria for the study were: 1) Patients whose histopathological examinations showed squamous cell carcinoma of the cervix; 2) Patients were completely treated for cervical carcinoma; 3) patients were in remission for at least 6 months’ period before recurrent lesions were suspected; 4) patients had both serum SCC Ag and CEA measured during the tumor surveillance program; 5) patients had 18F-FDG PET/CT scan done within an interval of less than 2 weeks following suspicion of recurrent lesions; 6) patients received no treatment between the interval from suspicion of cervical carcinoma recurrence and 18F-FDG PET/CT scan. The exclusion criteria were: 1) histopathological examinations showed adenocarcinoma or adenosquamous carcinoma of the cervix; 2) treatment was not cure-intent. The methods of enrolling patients were shown in Figure 1. A total number of 42 patients met the above criteria and were enrolled in this study.

Suspicion of cervical carcinoma recurrence

Suspicion of cervical carcinoma recurrences were based on patients presented with symptoms of tumor recurrence, abnormal findings on physical and internal examinations, abnormal results of cytological investigations, elevated levels of serum tumor markers and conventional imaging showed suspected recurrent lesions.

Tumor markers measurements

Serum samples were collected on each follow-up visit. The serum SCC Ag level was estimated using an
immunoradiometric assay kit (Imx, Abbott Diagnostics, Abbott Park, IL, USA). Serum CEA level was estimated using an automated chemiluminescence analyzer (ZT-480 Automated Chemiluminescence Analyzer, Beijing Savant Biotechnology Co., LTD., CHINA). The normal upper cut-off limit for SCC Ag and CEA were 1.5 ng/ml and 5.0 ng/ml, respectively.

Figure 1: Flowchart illustrating methods of enrolling patients in the study.

18F-FDG PET/CT scanning and image interpretation

Prior to 18F-FDG PET/CT scans, all patients were instructed to fast for at least 6 hours. 3.7MBq/kg body weight of 18F-FDG was then administered and the patients laid in a supine position for 1 hour in a dark and quiet room. Image acquisition was thus done using an integrated 18F-FDG PET/CT (Discovery PET/CT Elite, GE Medical Systems, USA). A whole body 18F-FDG PET/CT scanning consisted of CT scans prior to PET scans, in a supine position from the head to mid-thigh. The CT scan parameters were set to 120kV, 28.5-150mA, 0.5s per rotation and 39.37mm per rotation. The data obtained from the CT scans were constructed to images with a matrix of 512 x 512 and a slice thickness of 3.75mm. The PET scan was acquainted in a 3D imaging mode and the data obtained were reconstructed to image with a matrix of 192 x 192.

The CT and PET images were fused using Advanced workstation 4.5 (GE Medical Systems, Waukesha, Wisconsin, USA). The generated images were analyzed by two experienced nuclear medicine physicians, being aware of the patients’ clinical history and indication for 18F-FDG PET/CT. A semi-quantitative analysis was done by placing a VOI (Volume of Interest) over the suspected lesions to measure the SUVmax. The SUVmax was calculated by the formula: SUVmax = maximum voxel activity/ (injected dose/body weight).

A region was defined as malignant if the focal uptake of 18F-FDG was higher (SUVmax ≥2.5) than the surrounding tissue and were not associated with physiological uptake.

Confirmation of recurrences

The confirmation of recurrence for a positive PET/CT case was determined either by tissue biopsy or imaging studies or with second look surgery. As for the negative PET/CT cases, the patients were followed up for a short period by physical examination, cytological investigations, routine tumor markers as well as imaging modalities.

Data and statistical analysis

The following patients’ characteristics were retrospectively collected: age at first presentation, histopathology of cervical cancer, initial FIGO stage, treatment modalities, date of last treatment, date of suspicion of recurrence, date of PET/CT done, tumor markers (SCC Ag and CEA) during follow-up, means of suspecting recurrence, PET/CT reports, median SUVmax values and evidence of recurrence.

The PET/CT reports were classified as recurrence and no recurrence groups. Upon confirmation of the diagnosis, the cases were further classified into true-positive, false-positive, true-negative and false-negative. The overall sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of PET/CT for detection of recurrence of cervical carcinoma were determined. Fisher’s extract test or Pearson Chi-square test and Mann-Whitney U test were used for categorical and numerical data, respectively. Absolute and percentage frequencies were used to describe categorical data while means, median, standard deviation, and range were used to express continuous data. Statistical analyses were performed using SPSS software package (Version 23.0.0, SPSS, Chicago, IL, USA) and GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com. A p value < 0.05 was considered as statistically significant.
Results
A total of 42 patients with treated histopathologically proven squamous cell carcinoma of cervix underwent 18F-FDG PET/CT due to suspicion of recurrence by either symptoms, abnormal findings on physical and internal examinations, abnormal cytological reports, elevated levels of serum tumor markers or abnormal conventional imaging. The characteristics of patients enrolled in this study is summarized in Table 1.

Table 1. Characteristics of patients enrolled in the study.

| Characteristics | n   |
|-----------------|-----|
| Total patients  | 42  |
| Age (years)     | 47.62 (26-67) |
| Pathology       |     |
| Squamous cell carcinoma | 42 |
| Stage           |     |
| IA              | 2   |
| IB              | 13  |
| IIA             | 5   |
| IIB             | 15  |
| IIIA            | 1   |
| IIIB            | 5   |
| IVA             | 1   |
| Primary treatment |    |
| Conization      | 1   |
| Radical hysterectomy | 5 |
| Radical hysterectomy + Chemotherapy | 2 |
| Radical hysterectomy + Radiotherapy | 8 |
| Radical hysterectomy + Concurrent chemoradiotherapy | 2 |
| Neoadjuvant chemotherapy + Radical hysterectomy + Concurrent chemoradiotherapy | 17 |
| Concurrent chemoradiotherapy | 7 |
| Interval |     |
| Last treatment to suspicion of recurrence (months) | 40.6 (6-150) |
| Suspicion of recurrence to PET/CT (days) | 4.1 (0-12) |
| Elevated tumor markers |     |
| SCC Ag only     | 10  |
| CEA only        | 6   |
| SCC Ag and CEA  | 8   |
| None            | 18  |
| Confirmation of diagnosis |     |
| Biopsy          | 18  |
| Imaging (CT/MRI) | 16 |
| Tumor markers   | 1   |
| Follow-up       | 4   |
| Second look surgery | 3 |

Table 3. In this study, the overall patient-based sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of 18F-FDG PET/CT for detecting cervical cancer recurrence were 100%, 70.6%, 88.1%, 83.3% and 100%, respectively.

Table 2. Comparative analysis of 18F-FDG PET/CT patient-based performance of 42 treated cervical cancer patients in comparison with tumor markers.

| Elevated tumor markers | SCC Ag | CEA | SCC Ag + CEA | None | Total |
|------------------------|--------|-----|-------------|------|-------|
| TP                     | 9      | 2   | 8           | 6    | 25    |
| FN                     | 0      | 0   | 0           | 0    | 0     |
| FP                     | 1      | 4   | 0           | 5    | 6     |
| Total                  | 11     | 6   | 8           | 18   | 42    |
| Sensitivity (%)        | 100    |     |             |      |       |
| Specificity (%)        | 70.6   |     |             |      |       |
| Accuracy (%)           | 88.1   |     |             |      |       |
| PPV (%)                | 83.3   |     |             |      |       |
| NPV (%)                | 100    |     |             |      |       |
| Positive likelihood ratio | 3.4   |     |             |      |       |
| Negative likelihood ratio | 0     |     |             |      |       |

Table 3. Location of pathological 18F-FDG uptake in true positive cases.

| Sites of abnormal 18F-FDG uptake | n  |
|----------------------------------|----|
| Vaginal stump                    | 3  |
| Pelvic lymph nodes               | 10 |
| Inguinal lymph nodes             | 2  |
| Parametrium                      | 2  |
| Para-aortic lymph nodes          | 1  |
| Peritoneal deposits              | 2  |
| Colonic metastases               | 1  |
| Liver metastases                 | 5  |
| Mediastinal lymph nodes          | 4  |
| Pulmonary metastases             | 2  |

Diagnostic efficiencies of 18F-FDG PET/CT with each tumor marker and in combination of both tumor markers in detection of cervical cancer recurrence

Among the patients (n=42), 24 had elevated levels of SCC Ag and/or CEA and 18 had normal levels of both tumor markers. Of the elevated tumor markers (n=24), 10 had elevated levels of SCC Ag only, 6 had elevated levels of CEA only and 8 had elevated levels of both tumor markers. All 8 patients with both tumor markers elevated had developed recurrence. 9 out of 10 patients with elevated SCC Ag only and 2 out of 6 patients with elevated CEA only developed recurrence during the follow-up period. One patient with only increased SCC and 4 patients with only increased CEA levels were false positive, details of which are shown in Table 4. 6 patients...
developed recurrence and 12 did not within the normal levels of serum tumor markers group.

Table 4. Characteristics of false positive 18F-FDG PET/CT report.

| Tumor marker | Value (ng/ml) | Diagnosis                  |
|--------------|--------------|---------------------------|
| SCC Ag       | 4.30         | Radiation induced fibrosis |
| CEA          | 6.5          | Abscess                   |
| CEA          | 4.5          | Radiation induced fibrosis |
| CEA          | 31.65        | Abscess                   |

SCC Ag, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen

The accuracy of 18F-FDG PET/CT with elevated SCC Ag levels (90%; 9/10) was higher than 18F-FDG PET/CT with elevated CEA levels (33.3%; 2/6). The accuracy of 18F-FDG PET/CT in detecting recurrence was significantly different between elevated SCC Ag levels group and elevated CEA levels group (p=0.036). 18F-FDG PET/CT with combined SCC Ag and CEA elevation was more accurate (100%; 8/8) than 18F-FDG PET/CT with elevated SCC Ag levels, but there was no statistically significant difference between them (p=1.00). The PPV of a positive 18F-FDG PET/CT result with elevated levels of both tumor markers for the detection of recurrent cervical cancer was 100%. The NPV of a negative 18F-FDG PET/CT associated with normal levels of both tumor markers was 100%.

Correlation between tumor markers and SUV_max values

SUV_max showed a reasonable correlation with SCC Ag levels but not with CEA levels as shown in Figure 2A and 2B, respectively. The correlation between SUV_max and SCC Ag levels was statistically significant (p=0.03). No statistically significant correlation between SUV_max and CEA levels was observed (p=0.08). Moreover, there was so statistically significant correlation between the two tumor markers levels (p=0.23) as shown in Figure 2C.

Differences in tumor markers and SUV_max values among the recurrence and no recurrence group

The mean values of SCC Ag levels, CEA levels and SUV_max values were 11.3 ± 17.9 ng/ml, 14.6 ± 30.6 ng/ml and 7.3 ± 2.4, respectively in the recurrence group and 0.9 ± 0.9 ng/ml, 7.3 ± 15.7 ng/ml and 3.4 ± 3.7, respectively in the non-recurrence group. The differences of SCC Ag levels and SUV_max values were statistically significant (p<0.05 and p<0.05, respectively) between the recurrence and non-recurrence group. There was no statistically significant difference in CEA levels (p=0.05) between the recurrence and non-recurrence group. The distributions of SCC Ag, CEA, and SUV_max, respectively in recurrence versus non-recurrence group are illustrated in box-plot graphs (Figure 3).

Discussion

The aim of this retrospective study was to evaluate the role of 18F-FDG PET/CT in the diagnosis of recurrent squamous cell carcinoma of cervix in patients with elevated levels of SCC Ag and CEA. To our best knowledge, there is no previous study that reports the clinical value of 18F-FDG PET/CT in the recurrence of cervical cancer based on both tumor markers. Previous studies have reported the clinical value of 18F-FDG PET and 18F-FDG PET/CT to detect recurrence in patients treated for cervical cancer. However, those studies prioritized the use of 18F-FDG PET for detection of recurrence or included only patients with elevated tumor markers. Moreover, those studies showed the complementary role of 18F-FDG PET/CT and serum SCC Ag only for the diagnosis of recurrent cervical cancer [9, 15-28].

Figure 2. Scatter-plot graphs illustrating the correlation value between various measured parameters. (A) There was a reasonable correlation between SUV_max and SCC Ag levels (r=0.44). This correlation between SUV_max and SCC Ag levels was statistically significant (p<0.05). (B) There was a very low correlation between SUV_max and CEA levels (r=0.23). This correlation between SUV_max and CEA levels was not statistically significant (p=0.08). (C) There was a meaningless correlation between SCC Ag and CEA levels (r=0.19). No statistically significant correlation between the two tumor markers was observed (p=0.23). r, correlation coefficient; SCC Ag, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen; SUV_max, maximum standardized uptake value.
The principal finding of our study is that combining elevated SCC Ag and CEA levels with 18F-FDG PET/CT predicts the presence of recurrence and localization of relapse with 100% accuracy. The second major finding of this study is the high negative predictive value of 100% with negative 18F-FDG PET/CT scan combined with normal tumor markers levels. Thus, a negative 18F-FDG PET/CT scan with normal SCC Ag and CEA levels may be clinically reassuring of no cervical cancer recurrence.

This study has also found that there exists a reasonable correlation between SCC Ag levels and tumor volumes based on a SUV\text{max} value of 2.5 to determine tumor boundaries and volumes on 18F-FDG PET/CT. However, no such correlation was observed with CEA levels suggesting that cervical cancer recurrence with normal CEA levels would be demonstrated with 18F-FDG PET/CT or elevated CEA levels might be associated with negative 18F-FDG PET/CT scan with normal SCC Ag and CEA levels which is supported by no correlation between these tumor markers. However, elevated and non-elevated levels of tumor markers were considered in the study. Another reason that could explain this is the inclusion of CEA in the study that accounted for most of the false positive results. False positive results have also been reported in several previous reports and these results are explained by physiological hypermetabolism and reactive lymph nodes [8, 17, 18].

In the study, we also found six patients with normal levels of serum tumor markers who developed recurrences. As such, we are unable to say that normal levels of serum tumor markers can rule out recurrence. However, normal levels of both tumor markers associated with negative 18F-FDG PET/CT result could clinically reassure that a recurrence is absent.

In a retrospective study, Chong et al. [17] evaluated the clinical usefulness of 18F-FDG PET/CT in the detection of early recurrence in treated cervical cancer patients with unexplained elevation of serum tumor markers and the authors reported a similar finding that 18F-FDG PET/CT combined with elevated SCC Ag levels is more accurate than 18F-FDG PET/CT combined with elevated CEA levels which is supported by no correlation between these tumor markers. However, the discrepancy in accuracy values might be due to a difference in sample size and patients in their study measured either SCC Ag or CEA but not both.

Hu et al. [18] reported three cases of metachronous tumors that were considered as true positive. In our study, one metachronous tumor of adenocarcinoma of lung was observed that was regarded as true negative as 18F-FDG PET/CT distribution is well known for detecting of other diseases and/or metachronous tumor [32].

This study had certain limitations. Despite the combination of both tumor markers with 18F-FDG PET/CT providing a high accuracy of recurrence detection, it remains inapplicable for the clinical practice.
PET/CT is superior to 18F-FDG PET/CT with SCC Ag, the associated increase in diagnostic accuracy is uncertain due to small sample size. Other limitations were this was a retrospective study and the diagnosis of cervical carcinoma recurrence was based on follow-up.

Conclusions

Our study indicated that 18F-FDG PET/CT is highly sensitive for the diagnosis of recurrent cervical cancer regardless to type and level of tumor marker. The combination of elevated SCC Ag and CEA levels with 18F-FDG PET/CT improves the accuracy and localization of recurrent lesions to 100% thus offering maximum information for restaging and selecting appropriate salvage therapy for cervical cancer recurrence. Also, normal levels of both tumor markers with a negative 18F-FDG PET/CT result may clinically reassure that a recurrence is absent.

Abbreviations

18FDG PET/CT: 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography, SCC Ag: Squamous cell carcinoma antigen, CEA: Carcinoembryonic antigen, SUVmax: maximum standardized uptake value, PPV: positive predictive value, NPV: negative predictive value.

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Ethics committee approval

This retrospective study was approved by the Ethics Committee of Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, P. R. China.

Competing Interests

The authors have declared that no competing interest exists.

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