Research Paper

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 18F-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 recurrent cervical cancer 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 ([18]FDG PET) or 18F-Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography ([18]FDG 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 [18]FDG 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 [18]FDG uptake where maximum standardized uptake value (SUV_{max}) is the backbone [14]. Previous reports have shown the clinical value [18]FDG PET/CT in patients with elevated serum tumor markers during follow-up of cervical cancer. All these studies have evaluated the clinical significance of [18]FDG PET/CT with elevated SCC Ag or CEA in the detection of cervical cancer recurrence, but currently, there are no reports on [18]FDG 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 ^{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.

Materials and methods

Patients

We enrolled patients who underwent ^{18}F-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 ^{18}F-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 ^{18}F-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.
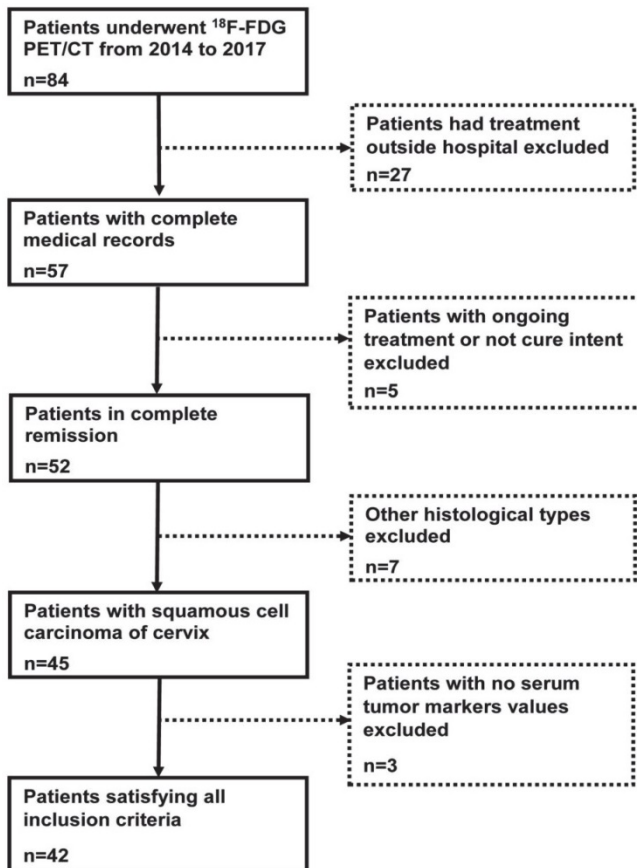

Figure 1: Flowchart illustrating methods of enrolling patients in the study.

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 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 SUV_{max}. The SUV_{max} was calculated by the formula: SUV_{max}=maximum voxel activity/ (injected dose/body weight).

A region was defined as malignant if the focal uptake of ¹⁸F-FDG was higher ($SUV_{max} \geq 2.5$) 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 SUV_{max} 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 ^{18}F-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

SCC Ag, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen
CT, computed tomography; MRI, magnetic resonance imaging

Diagnostic efficiency of ^{18}F-FDG PET/CT to detect cervical cancer recurrence

Of the 42 cervical cancer patients, ^{18}F-FDG PET/CT detected recurrent lesions in 30 patients and ruled it out in 12 patients. The ^{18}F-FDG PET/CT was true positive in 25 patients, false positive in 5 patients, true negative in 12 patients and false negative in none (Table 2). The common localization of ^{18}F-FDG uptake was in pelvic lymph nodes. ^{18}F-FDG PET/CT also found a second disease which was primary adenocarcinoma in lung. The distribution of pathological uptake of ^{18}F-FDG are summarized in Table 3. In this study, the overall patient-based sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of ^{18}F-FDG PET/CT for detecting cervical cancer recurrence were 100%, 70.6%, 88.1%, 83.3% and 100%, respectively.

Table 2. Comparative analysis of ^{18}F-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
TN	0	0	0	12	12
FP	1	4	0	0	5
FN	0	0	0	0	0
Total	10	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				

SCC Ag, squamous cell carcinoma antigen; CEA, carcinoembryonic antigen
TP, true positive; TN, true negative; FP, false positive; FN, false negative
PPV, positive predictive value; NPV, negative predictive value
*1 primary adenocarcinoma of lung included

Table 3. Location of pathological ^{18}F-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

^{18}F-FDG, 18F-Fluorodeoxyglucose

Diagnostic efficiencies of ^{18}F-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 ^{18}F-FDG PET/CT report.

Tumor marker	Value (ng/ml)	Diagnosis
SCC Ag	4.30	Radiation induced fibrosis
CEA	61.2	Granulation tissue following neck surgery
CEA	5.50	Abscess
CEA	7.45	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 ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET/CT in the recurrence of cervical cancer based on both tumor markers. Previous studies have reported the clinical value of ^{18}F-FDG PET and ^{18}F-FDG PET/CT to detect recurrence in patients treated for cervical cancer. However, those studies prioritized the use of ^{18}F-FDG PET for detection of recurrence or included only patients with elevated tumor markers. Moreover, those studies showed the complementary role of ^{18}F-FDG PET/CT and serum SCC Ag only for the diagnosis of recurrent cervical cancer [9, 15-28].
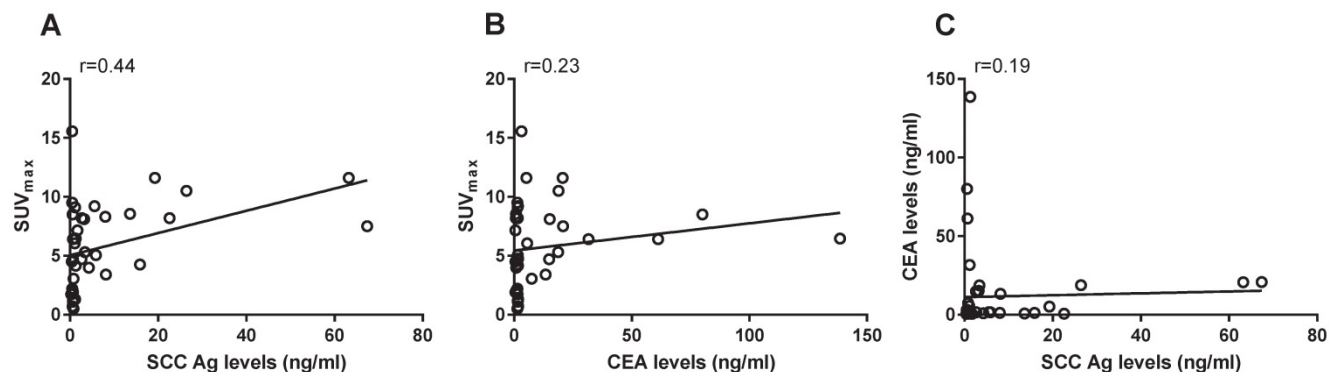

Figure 2. Scatter-plot graphs illustrating the correlation value between various measured parameters. (A) There was a reasonable correlation between SUV$_{max}$ and SCC Ag levels (r= 0.44). This correlation between SUV$_{max}$ and SCC Ag levels was statistically significant (p< 0.05). (B) There was a 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.
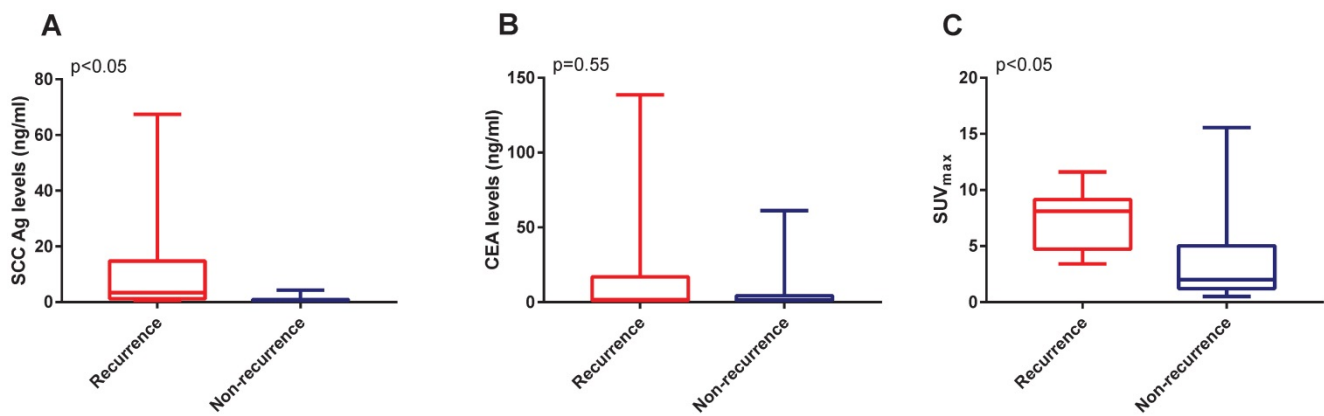
Figure 3. Box-plot graphs illustrating the distribution of SCC Ag, CEA and SUV$_{max}$ through recurrence and non-recurrence group. (A) There was statistically significant difference in SCC Ag levels through the recurrence and non-recurrence group (p< 0.05). (B) There was no statistically significant difference in CEA levels through recurrence and non-recurrence group (p=0.55). (C) There was statistically significant difference in SUV$_{max}$ values through the recurrence and non-recurrence group (p<0.05). 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 ^{18}F-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 ^{18}F-FDG PET/CT scan combined with normal tumor markers levels. Thus, a negative ^{18}F-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$_{max}$ value of 2.5 to determine tumor boundaries and volumes on ^{18}F-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 ^{18}F-FDG PET/CT or elevated CEA levels might be associated with negative ^{18}F-FDG PET/CT. As such, the combination of only CEA levels with ^{18}F-FDG PET/CT to detect cervical cancer recurrence during follow-up might not be appropriate for clinical practice.

Mike et al. and Forni et al. showed that elevated levels of SCC Ag can predict recurrence before the lesions become clinically apparent [29, 30]. However, these tumor markers cannot define the location of these lesions. In a comparative study between ^{18}F-FDG PET and CT/MRI, it was reported that ^{18}F-FDG PET was superior to CT in detecting small metastatic lymph nodes, whose principle is based on increased glycolysis levels in tumor cells [31]. Our study demonstrated a good overall patient-based sensitivity, accuracy, PPV and NPV of ^{18}F-FDG PET/CT in detecting recurrent cervical cancer that are consistent with previous studies [16-18, 22]. However, the specificity is lower (70.6%) compared to those studies. The reason might be due to the fact that both

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 tumors 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 ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET/CT combined with elevated SCC Ag levels is more accurate than ^{18}F-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 ^{18}F-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 ^{18}F-FDG

PET/CT is superior to ^{18}F-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 ^{18}F-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 ^{18}F-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 ^{18}F-FDG PET/CT result may clinically reassure that a recurrence is absent.

Abbreviations

[18]FDG PET/CT: 18F-Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography, SCC Ag: Squamous cell carcinoma antigen, CEA: Carcinoembryonic antigen, SUV$_{max}$: maximum standardized uptake value, PPV: positive predictive value, NPV: negative predictive value.

Acknowledgments

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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