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Research Paper

Complementary Roles of Squamous Cell Carcinoma Antigen and ^{18}F-FDG PET/CT in Suspected Recurrence of Cervical Squamous Cell Cancer

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Abstract

Purpose: To assess the clinical value of FDG PET/CT and evaluate the complementary roles of serum squamous cell carcinoma antigen (SCCAg) and FDG PET/CT in the diagnosis of suspected recurrent of cervical squamous cell cancer. *Methods:* Serum SCCAg levels were retrospectively reviewed in patients previously treated for cervical squamous cell carcinoma, who had suspected recurrence of cervical cancer and who had undergone FDG PET/CT scans. The clinical impact of elevated SCCAg (>1.5 ng/ml) and negative SCCAg (≤1.5 ng/ml) levels were analyzed based on the results of PET/CT and final diagnosis. *Results:* The overall patient-based sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of PET/CT for the detection of tumor recurrence or malignancy were 100% (86/86), 80.8% (21/26), 95.5% (107/112), 94.5% (86/91) and 100% (21/21), respectively. Of the 112 patients included in this study, recurrence or malignancy was detected by PET/CT in 62 of the 64 patients with elevated SCCAg, compared to 24 of the 48 patients with negative SCCAg levels. The overall patient-based PPV, NPV, sensitivity and accuracy of SCCAg for the detection of tumor recurrence or malignancy were 96.9% (62/64), 50% (24/48), 72.1% (62/86) and 76.8% (86/112), respectively. The five false-positive PET/CT results were all associated with patients with negative SCCAg levels. The PPV of positive PET/CT-associated elevated SCCAg for the detection of tumor recurrence or malignancy was 100% (62/62). The NPV of negative SCCAg-associated negative PET/CT was 100% (19/19). *Conclusions:* Serum SCCAg evaluation and FDG PET/CT imaging can be complementary techniques in cases of suspected recurrent cervical squamous cancer. Positive PET/CT with elevated SCCAg can predict recurrence. Although PET/CT cannot confidently be deferred due to a negative SCCAg test, the possibility of a false-positive PET/CT in those cases may have diagnostic importance.

Key words: Squamous cell carcinoma antigen; Cervical squamous cancer; Recurrence; FDG PET/CT; False positive

Introduction

Squamous cell carcinoma antigen (SCCAg) is a useful tumor marker in patients with cervical squamous cell cancer. Elevated SCCAg levels have been correlated with cervical cancer recurrence [1,2]. Furthermore, increases in SCCAg levels could be detected before clinical signs of relapse [3,4]. However, it is unclear whether elevated SCCAg can confirm recurrence and negative SCCAg exclude recurrence;

therefore, the correct interpretation of different SCCAg levels, particularly, in cases of suspected recurrence, remains a clinical challenge.

Several studies have demonstrated the clinical value of fluorodeoxyglucose (18F)-positron emission tomography (FDG-PET) or integrated PET/computed tomography (PET/CT) in patients with cervical cancer who are found to have unexplained elevated serum SCCAg or carcinoembryonic antigen (CEA) during follow-up [5–7]. Conversely, there are currently no reports on the complementary roles of PET/CT and different serum SCCAg levels in suspected recurrent cervical squamous cell cancer.

In this study, we evaluated FDG PET/CT in relation to serum SCCAg levels and demonstrated the diagnostic value of complementary testing of serum SCCAg and PET/CT in suspected recurrent cervical squamous cell cancer.

Materials and methods

Patient selection and evaluation of suspected recurrence

The medical records of female patients who had a suspected recurrence of previously treated cervical cancer and who had undergone FDG PET/CT between July 2005 and December 2011 were retrospectively reviewed. The eligibility requirements for inclusion were as follows: histologically confirmed cervical squamous cell carcinoma according to The International Federation of Gynecology and Obstetrics (FIGO) classification system, SCCAg levels measured regularly during post-therapy surveillance or in cases with suspected recurrence, a time interval of <2 weeks between measuring SCCAg and the PET/CT scan, no treatment for cancer between the SCCAg measurement and the PET/CT scan and a minimum follow-up period of 12 months following PET/CT.

The criteria for suspected recurrence were as follows: patients presented symptoms of tumor recurrence, routine imaging showed suspected recurrent lesions, abnormal results were observed during routine physical and gynecological examinations and elevated levels of serum tumor markers were recorded during routine surveillance.

FDG PET/CT imaging

Scanning was performed using a dedicated PET/CT system (Discovery ST-16; GE Medical Systems, Milwaukee, WI, USA). The patients fasted for 6 h before being intravenously injected with ^{18}F-FDG (4.4–7.4 MBq/kg). They then rested, lying down, in a dark room for 45–60 min prior to PET/CT imaging. The patients were scanned in a supine position from the skull to the middle part of the femur. CT was performed prior to PET, and the resulting data were used to generate a PET attenuation correction map. PET images were reconstructed with a slice thickness of 3.75 mm using the Ordered Subsets Expectation Maximization (OSEM) iterative image reconstruction method. PET, CT and fused PET/CT images were generated for review on a Xeleris computer workstation (GE Medical Systems, Milwaukee, WI, USA).

All interpretations were performed retrospectively by two experienced nuclear medicine physicians with knowledge of the patient's clinical history and the reason for the PET/CT examination. An area was defined as malignant if the intensity of focal ^{18}F-FDG uptake was higher than that of the surrounding tissues and was unrelated to physiological or benign processes. Semiquantitative analysis was not performed in this study.

SCCAg assay

Serum SCCAg levels were analyzed using an automated chemiluminescence immunoassay (CLIA) system (i2000, Abbott, USA) according to the manufacturer's instructions. The recommended cutoff level of 1.5 ng/ml was applied. Elevated SCCAg was defined as >1.5 ng/ml, and negative SCCAg was defined as ≤1.5 ng/ml.

Clinical evaluation of recurrence

The final diagnosis was verified by PET/CT-guided surgery or by biopsy and clinical follow-up findings. Recurrent disease was confirmed if the following criteria were satisfied: positive histopathological results, evidence of progressive disease as determined by serial imaging and subsequent partial or complete remission as a result of therapy following PET/CT. In addition, patients were also classified as having recurrent disease if they presented multi-metastases on PET/CT images but were too weak to complete their planned therapy and were therefore discharged. For clinical confirmation of an absence of recurrence, histopathologically negative results, normal physical and gynecological examinations and negative findings from follow-up imaging were required.

Results

Clinical characteristics of the subjects

A total of 112 patients with cervical squamous cell cancer who satisfied the selection criteria were recruited in this study. The median age was 47 years (range, 26–76 years). According to the FIGO classification, 44 patients were at stage I, 55 were at stage II, 11 were at stage III and 2 patients had carcinoma in situ (CIS). All the patients had undergone successful curative treatment, including radical surgery (n = 15),

surgery plus radiotherapy or chemotherapy (n = 28), surgery plus chemoradiotherapy (n = 41), radical radiotherapy or radical radiotherapy plus chemotherapy (n = 26), simple hysterectomy (n = 1) or cervical conization (n = 1). The median time from final treatment to the PET/CT scan was 12 months.

The median serum SCCAg level in the total cohort of 112 patients was 2.1 ng/ml (range, 0~70 ng/ml). Sixty-four patients had elevated SCCAg levels, with a median level of 5.7 ng/ml (range, 1.6~70 ng/ml). Forty-eight patients had negative SCCAg levels, where the median level was 0.3 ng/ml (range, 0~1.5 ng/ml).

PET/CT, histopathology and clinical follow-up

The PET/CT, histopathological results and results of clinical follow-up are given in Table 1. Positive PET/CT results were observed in 91 patients. Of these, 83 presented with recurrence, three had primary lung squamous cell carcinoma and five had benign diseases. There were five false-positive PET/CT results. There were 21 patients with negative PET/CT results. The overall patient-based sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of PET/CT for the detection of tumor recurrence or malignancy were 100% (86/86), 80.8% (21/26), 95.5% (107/112), 94.5% (86/91) and 100% (21/21), respectively.

Evaluation of the complementary roles of serum SCCAg with PET/CT

The results of PET/CT in relation to patient serum SCCAg levels and final diagnoses are given in Table 2. Elevated SCCAg was detected in 64 patients; of these, 62 (96.9%) had positive PET/CT results and were confirmed to have recurrence or malignancy. The remaining two patients with elevated SCCAg had negative PET/CT scans and were tumor-free during a 2-year follow-up without receiving further cancer therapy. In contrast, only 24 (50%) of the 48 patients with negative SCCAg levels were found to have recurrence or malignancy by PET/CT. The overall patient-based PPV, NPV, sensitivity and accuracy of SCCAg for the detection of tumor recurrence or malignancy were 96.9% (62/64), 50% (24/48), 72.1% (62/86) and 76.8% (86/112), respectively. In addition, the five patients with false-positive PET/CT results were found to be SCCAg-negative. The PPV of positive PET/CT-associated elevated SCCAg for the detection of tumor recurrence or malignancy was 100% (62/62). The remaining 19 patients were both PET/CT-negative and SCCAg-negative. The NPV of negative SCCAg-associated negative PET/CT was 100% (19/19).

Discussion

The purpose of this retrospective study was to establish whether FDG PET/CT imaging and evaluation of serum SCCAg levels in patients can be complementary for confirming suspected recurrent cervical squamous cell cancer.

In this study, we evaluated FDG PET/CT in relation to both elevated serum SCCAg and negative serum SCCAg in suspected cases of recurrent cervical squamous cell cancer. The results demonstrated the diagnostic value of complementary testing for serum SCCAg and PET/CT. Several studies have reported the clinical value of FDG-PET or FDG PET/CT in patients with cervical cancer who have unexplained elevated levels of serum SCCAg or CEA during follow-up [5–7]. However, those studies were performed using PET or only included patients with elevated tumor markers or who did not show complementary values of FDG PET/CT and serum SCCAg for the diagnosis of recurrent cervical squamous cell cancer.

Table 1. Patient-based results of PET/CT, and histopathological and follow-up findings.

Results	Histopathological and follow-up findings (no. of patients)					
	Recurrence	Primary lung squamous cell cancer	Radiation enterocolitis	Abscess	Granulation tissue	Negative findings
PET/CT(+)	83	3	1	3	1	0
PET/CT(-)	0	0	0	0	0	21

Table 2. Patient-based results of PET/CT, serum SCCAg levels and final diagnosis.

Results	Elevated serum SCCAg (no. of patients)			Negative serum SCCAg (no. of patients)		
	Recurrence or malignancy	Benign diseases	Negative findings	Recurrence or malignancy	Benign diseases	Negative findings
PET/CT(+)	62*	0	0	24**	5	0
PET/CT(-)	0	0	2	0	0	19

* Two primary lung cancer patients were included.
** One primary lung cancer patients was included.

Studies have demonstrated the clinical value of FDG-PET or FDG PET/CT in evaluating recurrent cervical cancer [8–18]. Our results supported these studies by showing that FDG PET/CT had high sensitivity, accuracy, PPV and NPV in the detection of recurrent cervical cancer during post-therapy surveillance. False-negative and false-positive PET/CT results have also been reported previously [15, 18]. Although there were no false-negative PET/CT results in our data, we had five false-positive PET/CT results in our study. Of potential significance was that these false-positive PET/CT results were associated with five patients who had negative serum SCCAg levels. The possibility of observing a false-positive PET/CT result in patients with negative SCCAg levels may have diagnostic implications. We also found that all 62 patients in this study with a positive PET/CT and elevated SCCAg were identified to have tumor recurrence or malignancy. Positive PET/CT-associated elevated SCCAg had a higher PPV in cases of suspected recurrent cervical squamous cell cancer compared to positive PET/CT alone.

Micke et al. showed that an increase in SCCAg level preceded the clinical diagnosis of relapse, with a lead time ranging from 1–16 months [3]. Similarly, Forni et al. documented an elevation of SCCAg in 79.1% of cervical cancer recurrences before symptoms appeared, and of these, 89.5% (PPV) developed recurrence [2]. In our study, 96.9% patients with elevated SCCAg levels were confirmed to have recurrence or malignancy. The higher PPV in our study may have been due to the conventional imaging modalities used in the earlier studies, such as chest X-rays, CT and magnetic resonance imaging (MRI). CT and MRI rely on size criteria and morphological changes for detecting lesions; therefore, small or normal-sized lymph node metastases can be missed. Furthermore, recurrent lesions can occur anywhere in the body, but local imaging techniques are limited in their ability to detect metastases beyond their scanning range. Another factor that may have contributed to the higher sensitivity in our study was that our study group included patients who had their SCCAg levels assessed as a response to suspected recurrent symptoms.

Despite the high sensitivity (96.9%) of PET/CT in our study among patients with elevated SCCAg levels, recurrence or malignancy was only detected in 50% of patients with negative SCCAg levels. As such, we were unable to verify that negative SCCAg levels indicate an absence of tumor recurrence. However, negative SCCAg associated with negative PET/CT could indicate that a recurrence is absent.

Two patients in our study with elevated SCCAg levels and negative PET/CT were tumor-free during a 2-year follow-up. Elevation of SCCAg has been reported in nonmalignant diseases, such as renal failure, lung pathologies and head and neck diseases [5, 19]. This suggests that PET/CT may have value in excluding patients with elevated SCCAg who present with nonmalignant diseases during follow-up of cervical squamous cell cancer.

Although our results have demonstrated that PET/CT has value in detecting suspected recurrent cervical squamous cell cancer based on different SCCAg levels, this study had the following limitations: it was a retrospective study; the SCCAg measurements were not restricted to regular post-therapy surveillance but also included cases where recurrence was suspected; the complementary roles of SCCAg and PET/CT were solely evaluated in patients with suspected recurrent cervical squamous cell cancer; the clinical impact of SCCAg could not be analyzed fully; tissue samples were not available for the final diagnosis in all cases; and the final diagnosis in some patients was based on clinical follow-up findings.

In conclusion, serum SCCAg levels and FDG PET/CT imaging can be complementary for verifying cases of suspected recurrent cervical squamous cancer. Positive PET/CT and elevated SCCAg are predictive of recurrence; therefore, PET/CT can be valuable in patients with elevated SCCAg levels. In contrast, PET/CT cannot be confidently deferred on the basis of a negative SCCAg test; however, the possibility of a false-positive PET/CT result may have diagnostic implications in patients with negative SCCAg levels.

Competing Interests

The authors have declared that no competing interest exists.

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