A study on the clinical value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography combined with serum squamous cell carcinoma antigen in diagnosing recurrence/metastases in patients with early metaphase cervical cancer

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Received November 29, 2019; Accepted July 23, 2020

DOI: 10.3892/ol.2021.13007

Abstract. Cervical cancer (CC) is the most common female genital tract malignancy, with repercussions on the psycho-physiological health of female patients. Patients with CC are faced with a high risk of postoperative recurrence and metastases. The present study aimed to evaluate the clinical value of 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) combined with serum squamous cell carcinoma antigen (SCC-Ag) in the diagnosis of postoperative recurrence/metastases in patients with early stage CC. This was a prospective follow-up study on 246 patients who received surgery for early stage CC. The results of clinical follow-up and pathological examination were taken as the gold standard. The diagnostic sensitivity, specificity, positive predictive value, negative predictive value and area under the receiver operating characteristic (ROC) curve were calculated for PET/CT, serum SCC-Ag determination and the combined PET/CT and serum SCC-Ag method. Results demonstrated that 90.11% patients completed the follow-up, and the median follow-up time was 22 months (range, 7-42 months). Tumor recurrence or metastasis was confirmed in a total of 137 patients (55.7%), including 18 deaths. The diagnostic sensitivity of PET/CT scan combined with serum SCC-Ag determination for postoperative metastases/recurrence in patients with early stage CC was 93.43% (95% CI, 0.875-0.967). The specificity was 92.67% (95% CI, 0.856-0.965), the positive predictive value was 94.12% (95% CI, 0.884-0.972), the negative predictive value was 91.81% (95% CI, 0.846-0.959) and the area under the ROC curve was 0.930±0.019 (95% CI, 0.893-0.968; P<0.001). The results also revealed that the serum SCC-Ag level was positively correlated with SUVmax (r=0.458; P<0.001). The results from the present study demonstrated that for patients with early metaphase CC, PET/CT scan combined with serum SCC-Ag determination during the follow-up was capable of earlier, more comprehensive and more accurate detection of recurrence/metastatic lesions, which is of high clinical application value.

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Key words: cervical cancer, positron emission tomography/computed tomography, metastases, recurrence

Introduction

Cervical cancer (CC) is the most common female genital tract malignancy, and has an impact on the psychophysiological health of female patients (1). CC ranks fourth in terms of incidence and mortality rates among all malignancies in women globally; it was estimated that there were 569.8 thousand newly diagnosed cases of CC and 311.4 thousand deaths related to CC in 2018 in China (2). Among the cases of mortality, 85% were found in developing countries (2,3). The incidence of CC in China is ~10.30/100,000 individuals, and the mortality is 2.62/100,000 individuals. The incidence and mortality rates of CC rank the seventh and eighth among all female malignancies, respectively in China (4). CC remains the primary disease threatening the health and life of Chinese women.

Clinical staging of CC by the International Federation of Gynecology and Obstetrics is still highly subjective and has limitations (5). By using this staging system, the high-risk factors influencing prognosis, such as infiltration of the parametrium and lymphatic vessels, vaginal involvement and lymph node metastases, are not easy to distinguish and the heterogeneity is large (6,7). To address the aforementioned limitations of FIGO staging system, MRI, CT and PET/CT scans have been used as auxiliary diagnostic tools for staging, efficacy

observation and evaluation of failure mode (an effective tool for risk assessment and improvement), prognosis and efficacy of CC treatment (8-10). ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is a state-of-the-art molecular imaging technique, which not only provides precise anatomical information, but also detects the metabolic changes of the tissues and organs at the molecular level. This technique has been increasingly applied to the diagnosis and treatment of CC (9,11,12). In a previous systematic review and meta-analysis of 72 studies that included 5,042 patients (13), the diagnostic performance of PET/CT scan for lymph node metastases for early stage CC was better than that of MRI and CT scans. The diagnostic sensitivity and specificity of PET/CT scan were 74.7% (95% CI, 63.3-84.0) and 97.6% (95% CI, 95.4-98.9), respectively. The value of MRI and CT were 55.2% (95% CI, 49.2-61.7), 57.5% (95% CI, 53.5-61.4) and 93.2% (95% CI, 91.4-94.0), 92.3% (95% CI, 91.1-93.5), respectively.

Serum tumor markers have been gradually introduced in the early diagnosis of CC. Some genes are uniquely expressed in different cancer types, and squamous cell carcinoma antigen (SCC-Ag) is the most common marker for CC (14,15). A number of studies have shown that serum SCC-Ag levels are associated with staging, tumor size, degree of cervical invasion and lymph node metastases in squamous cell carcinoma of the cervix (16-19).

In the present study, a prospective follow-up investigation was performed on patients who received treatment for early metaphase CC. The follow-up lasted for 7 to 42 months. The purpose of the study was to discuss the clinical value of PET/CT combined with serum SCC-Ag in diagnosing postoperative recurrence and metastases in patients with CC. The research findings shed new light on an earlier, more accurate and more comprehensive detection method for recurrent/metastatic CC lesions, and also on the development of subsequent individualized treatment to improve the survival rate and quality of life of patients with CC.

Patients and methods

Patients. The present study conformed to the Declaration of Helsinki and was approved by the Ethics Committee of Southwest Medical University (Luzhou, China). Early and middle stage patients with CC who received treatment at The Affiliated Hospital of Southwest Medical University between January 1st 2015 and December 31st 2017 and who had complete data were followed up. The inclusion criteria were as follows: i) confirmed as CC by surgical pathology, including squamous cell carcinoma, adenosquamous carcinoma and adenocarcinoma of the cervix; ii) classified as stage IA-III B according to the 2009 FIGO staging system (5); iii) IA-IIA patients were mainly treated with surgery (extensive panhysterectomy with pelvic lymph node dissection); iv) IIB-IIIB patients were mainly treated with platinum-based chemotherapy or radiotherapy; v) no contraindications for imaging, with consent for PET/CT; vi) no other malignancies, and no diseases influencing serum SCC-Ag levels, such as dermatological and respiratory diseases. The exclusion criteria were as follows: i) distant metastases confirmed before treatment; ii) patients who were pregnant or lactating. A total of 273 patients were eligible and provided written informed consent.

Methods and follow-up. All included patients were followed up once every 2 months in the first 6 months and then once every 3 months. The follow-up was ≥6 months, with the last follow-up conducted in June 2019. During the follow-up, 19 patients left the study, including 9 patients who did not receive PET/CT scan, and 8 patients were lost to follow-up. Thus, 246 patients were included in the final results. A total of 90.11% of patients completed the follow-up, and the median follow-up duration was 22 months (range, 7-42 months).

During each follow-up, the serum SCC-Ag level was detected. For the first two follow-up visits, PET/CT was immediately performed for patients suspected of tumor recurrence and metastases based on clinical manifestations, gynecological examination, transvaginal ultrasonography, routine imaging examination or serum tumor marker determination. For those patients who did not receive a PET/CT scan during the first two follow-up visits, a PET/CT scan was performed in the third follow-up visit. The flow diagram of the follow-up and study is shown in Fig. 1.

Serum SCC-Ag determination. The serum SCC-Ag level was detected at 3 days before the PET/CT scan (regardless of whether such a test had been performed previously). From each patient, 3 ml of venous blood was collected, and the plasma was separated to harvest the serum (placed in water bath for 30 min at 7˚C and centrifuged at 4,000 x g for 10 min at 4˚C). The serum SCC-Ag level was detected by using a fully automated microplate reader (Abbott i-2000 automatic immune analyzer) and quantitative assay kit for SCC-Ag (cat. no. CF051163; Tellgen Corp.). The normal SCC-Ag range was 0-1.5 ng/ml. The presence of recurrence or metastases was considered if SCC-Ag >1.5 ng/ml.

PET/CT scan. The PET/CT scan was performed with the GEMINI TF16 PET/CT scanner (Philips Healthcare). ^{18}F-FDG was provided by HTA Co., Ltd., with radiochemical purity >95%. Before the scan, the patients fasted for at least 6 h and required to maintain a stationary status. Plasma glucose levels were determined in the peripheral venous blood to ensure that the blood glucose level was kept at 3.9-11.1 mmol/l. The contrast agent (^{18}F-FDG) was injected intravenously at a dose of 3.7-5.5 MBq/kg of body weight, and then the patients lay down to rest in a quiet room for 45 to 60 min. During the rest, the patients were told to drink purified water (~1,200 ml) and then empty their bladder prior to the PET/CT scan. The patients took a supine position on the examination couch. During the body scan, the patients were told to fold the two forearms over the forehead, and for the head scan (both upper limbs were flat on both sides of the body during head scan), the patients were to breathe smoothly and keep an immobile body position, so that the CT and PET images could be fused perfectly. A low-dose plain CT scan was first performed (voltage, 120 kV; current, 10 mA; rotation time of the bulb tube, 0.3 sec per round; slice thickness, 5 mm). The scan scope was from the top of the skull to the middle and upper segments of the thigh. Next, PET images (3D model) were collected and reconstructed. Usually, each scan was performed at 6-8 bed

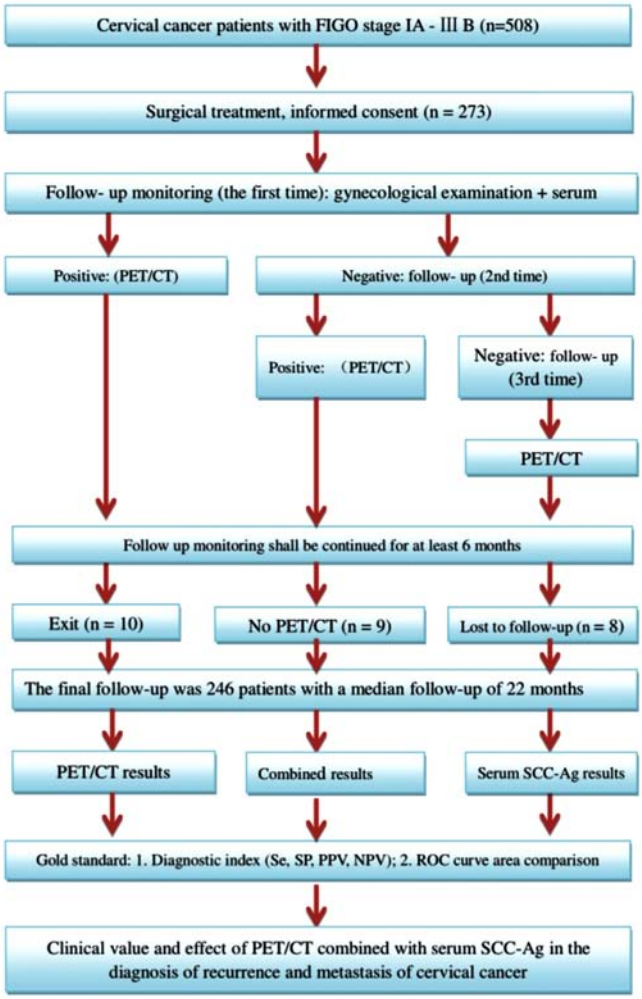

Figure 1. Flow diagram of the follow-up and study. FIGO, International Federation of Gynecology and Obstetrics; SCC-Ag, squamous cell carcinoma antigen; PET/CT, positron emission tomography/computed tomography; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver operating characteristic.

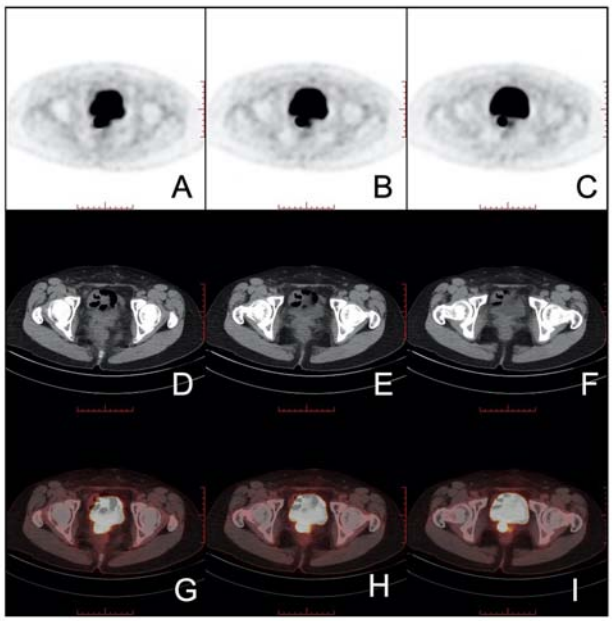

Figure 2. Representative PET/CT scan images of postoperative tumor recurrence and metastases of a patient with cervical cancer. (A-C) PET images. (D-F) CT images. (G-I) Fusion images of PET and CT images. The patient was 44 years old. In the upper right side of the vaginal stump, an irregular and slightly low-density mass shadow is seen, the uptake of imaging agent (^{18}F-FDG) is increased, and the boundary between the mass and bladder and rectum is unclear. PET, positron emission tomography; CT, computed tomography.

positions (depending on the height of patients); the collection time per bed position was 2-3 min for the body surface and 3-5 min for the brain.

The images were reviewed independently by two nuclear medicine physicians with >15 years of experience. A consensus was reached by discussion in cases where opinion diverged. If the former 2 doctors had differing opinions, another doctor (chief physician with >20 years of experience) made the final decision. The quantitative analysis was performed with a semi-quantitative indicator, the maximum standardized uptake value (SUV_{max}), which is now widely used in the clinic. Lesions with high ^{18}F-FDG uptake were located compared to that in comparable normal contralateral structures and/or surrounding soft tissues. The region of interest was delineated along the periphery of the lesions on the most clearly visualized sections in terms of radioactivity uptake. The computer workstation then automatically calculated the mean SUV (SUV_{mean}) and SUV_{max}. The presence of metastases and tumor recurrence was considered if the SUV_{max} was ≥2.5. For patients with multiple lesions, representative lesions were chosen to determine the SUV_{max}. For the qualitative analysis, the existence of residual or recurrent lesions was considered if soft-tissue density shadows appeared in the primary site, with abnormally high radioactivity uptake. In addition, if new lesions were revealed by scans of the whole body and other positions, with abnormally high radioactivity uptake, the presence of metastases was considered. Typical PET/CT images of postoperative metastases and recurrence in patients with CC are shown in Fig. 2; the images of those without postoperative metastases and recurrence are shown in Fig. 3.

Combined diagnostic method. When PET/CT was combined with serum SCC-Ag determination, any positive indicator was deemed positive for the combined diagnostic method. If both tests were negative, no tumor recurrence or metastasis was considered.

Gold standards. Criteria for metastases or recurrence of CC were as follows: i) the patients received a secondary surgery or puncture, and the diagnosis was confirmed by pathology; and ii) the patients did not receive a secondary surgery or puncture, but a judgment was made with reference to the follow-up results (medical history, gynecological examination, cytological smear of vaginal stumps, tumor markers and imaging). The patients with metastases or recurrence received follow-up examinations for >6 months, and the lesions increased in number or volume progressively. The results of the PET/CT scan and serum SCC-Ag determination were compared against the final clinical diagnosis made by surgical pathology and follow-up. Those with positive results from the PET/CT scan and serum SCC-Ag determination were considered true-positive cases if tumor recurrence was confirmed within 3 months by surgical

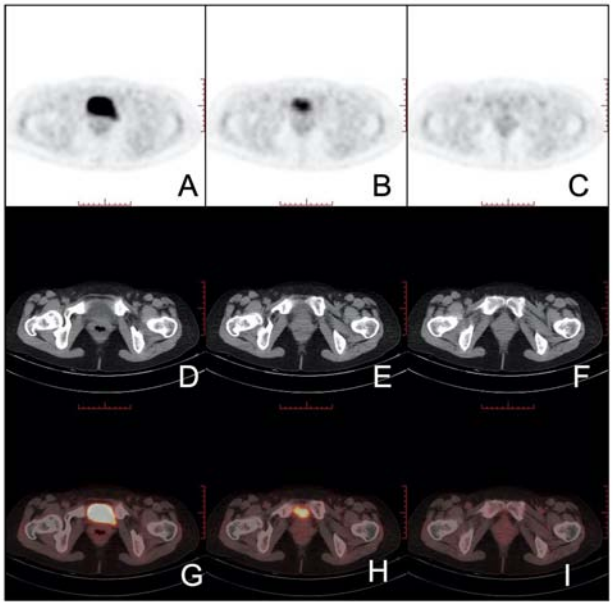

Figure 3. Typical PET/CT scan images of a patient with no postoperative tumor recurrence and metastases for cervical cancer. (A-C) PET images. (D-F) CT images. (G-I) Fusion images of PET and CT images. The patient was 51 years old. After cervical CC surgery, there is an absence of the uterus and bilateral appendages, and there is no obvious abnormality in the distribution of imaging agents in the corresponding areas. PET, positron emission tomography; CT, computed tomography.

pathology; otherwise, they were regarded as false-positive cases. If no lesions were found during the 3-month follow-up for the negative patients, they were considered true-negative cases, while the presence of lesions meant that they were considered false-negative cases.

Statistical analysis. SPSS 20.0 software (IBM Corp.) was used to perform the statistical analysis. For the baseline information of the patients, the counts were expressed as means (percentages) and the quantitative data were expressed as mean ± standard deviation. The results of pathology and clinical follow-up were taken as the gold standard for diagnosis. The consistency between the results of different diagnostic methods and the gold standard was measured by κ test. K value ≥0.7 indicated high consistency, 0.4-0.7 indicated moderate consistency and <0.4 indicated low consistency. The diagnostic sensitivity, specificity, positive predictive value and negative predictive value were calculated for PET/CT, serum SCC-Ag determination and the combined method. The accuracy [accuracy=(true positive + true negative)/total sample size x100%) and misdiagnosis rate (misdiagnosis rate=false positive/true negative x100%] of the diagnostic results were calculated. The diagnostic results of the three methods were compared by the χ^2 test (McNemar χ^2 test was used for paired data and Pearson χ^2 test was used for independent sample data). To account for multiple comparisons, Bonferroni correction was applied to correct all the P-values. The diagnostic efficacy was compared by the ROC curve analysis. CIs for area under the ROC curve values were estimated on the basis of a 95% confidence level. The areas under the ROC curve were compared by the Z test. The scatter plots to establish the association between SUV_{max} and serum SCC-Ag levels in the patients with CC were also drawn, and the correlation between the two was analyzed by Pearson's correlation analysis. P<0.05 was considered to indicate a statistically significant difference.

Table I. Baseline information of cervical cancer patients (n=246).

Characteristic	Value
Mean age (range), years	51.4±10.2 (29-73)
FIGO clinical staging, n (%)	
IA	22 (8.9)
IB	45 (18.3)
IIA	39 (15.9)
IIB	55 (22.4)
IIIA	27 (11.0)
IIIB	58 (23.6)
Pathological classification, n (%)	
Squamous cell carcinoma	210 (85.4)
Adenocarcinoma	26 (10.6)
Adenosquamous carcinoma	10 (4.1)
Tumor size, n (%)	
≥4.6 cm	130 (52.8)
<4.6 cm	116 (47.2)
Metastases or recurrence, n (%)	
Yes	137 (55.7)
No	109 (44.3)
PET/CT scan, n (%)	
Positive	126 (51.2)
Negative	120 (48.8)
Serum SCC-Ag determination, n (%)	
Positive	151 (61.4)
Negative	95 (38.6)

FIGO, International Federation of Gynecology and Obstetrics; PET/CT, positron emission tomography/computed tomography; SCC-Ag, squamous cell carcinoma antigen.

Results

Baseline information of patients with CC. The 246 patients with CC receiving treatment were aged 39 to 73 years old, with a mean age of 51.4±10.2 years. According to the FIGO staging system, there were 22 patients with stage IA (8.9%), 45 patients with stage IB (18.3%), 39 patients with stage IIA (15.9%), 55 patients with stage IIB (22.4%), 27 patients with stage IIIA (11.0%) and 58 patients with stage IIIB (23.6%) disease. Pathology of the primary lesions confirmed squamous cell carcinoma in 210 patients (85.4%), adenocarcinoma in 26 patients (10.6%) and adenosquamous carcinoma in 10 patients (4.1%) (Table I).

There were 130 patients with primary lesions ≥4.6 cm (52.8%) and 116 patients with primary lesions <4.6 cm (47.2%).

During the follow-up, tumor recurrence or metastases were confirmed in a total of 137 patients (55.7%), including 18 deaths. The average SUV_{max} was 7.17±6.88. PET/CT scan revealed

Table II. Comparison of postoperative metastases and recurrence diagnosed by the PET/CT, serum SCC-Ag or combined methods.

Examination method	Examination results	Pathology and follow-up		κ coefficient	P-value
		Positive, n	Negative, n		
PET/CT	Positive	116	10	0.747	<0.001
	Negative	21	99		
Serum SCC-Ag	Positive	123	28	0.649	<0.001
	Negative	14	81		
Combined method	Positive	128	8	0.860	<0.001
	Negative	9	101		

PET/CT, positron emission tomography/computed tomography; SCC-Ag, squamous cell carcinoma antigen.

Table III. Comparison of diagnostic efficacy of the combined diagnostic method.

Examination method	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)
PET/CT	84.67% (0.722-0.900)	90.83% (0.834-0.953)	92.06% (0.855-0.959)	82.50% (0.742-0.886)
Serum SCC-Ag	89.78% (0.831-0.941)	74.31% (0.649-0.819)	81.45% (0.741-0.871)	85.26% (0.762-0.914)
Combined method	93.43% (0.875-0.967)	92.67% (0.856-0.965)	94.12% (0.884-0.972)	91.81% (0.846-0.959)
P1[a]	0.043[b]	0.815[b]	0.511[c]	0.036[c]
P2[a]	0.405[b]	<0.001[b]	<0.001[c]	0.138[c]

[a]Bonferroni correction was applied to correct the P-values, α'=0.05/2=0.025. P<0.025, significantly different from the combined method. [b]The statistical analysis used McNemar's χ^2 test; [c]The statistical analysis used Pearson's χ^2 test. PET/CT, positron emission tomography/computed tomography; SCC-Ag, squamous cell carcinoma antigen; P1, PET/CT compared with combined method; P2, serum SCC-Ag compared with combined method.

126 positive results (51.2%). The average serum SCC-Ag level was 5.68±4.68 ng/ml, and 151 patients (61.4%) were positive according to serum SCC-Ag determination (Table I).

Comparison of the results of the three diagnostic methods. The results of pathological examination and follow-up were taken as the gold standard, and the diagnostic results of the three methods (PET/CT scan, serum SCC-Ag determination and the combination of both) were compared against the gold standard. As shown in Table II, with the PET/CT scan, 10 patients had a false-positive diagnosis, with a misdiagnosis rate of 5.74%; 21 patients were affected by a false-negative diagnosis, with a missed diagnosis rate of 8.14%; and the accuracy of PET/CT scan method was 87.39%. With the serum SCC-Ag detection method, 28 patients had a false-positive diagnosis, with a misdiagnosed rate of 16.09%. A false-negative diagnosis affected 14 patients, with the missed diagnosis rate of 4.42%. The accuracy of this method was 82.92%. For the combined method, 8 patients had a false-positive diagnosis, with a misdiagnosis rate of 4.59%, while a false-negative diagnosis affected 9 patients, with a missed diagnosis rate of 3.49%. The accuracy of this combined method was 93.09%. The results of the three diagnostic methods were compared against those of pathological examination. According to the consistency test, the κ coefficient was 0.747 for PET/CT scan, and 0.860 for the combined method. The serum SCC-Ag method had general consistency (κ coefficient <0.7). A statistically significant difference was observed for both PET/CT and combined methods, indicating high consistency of these two methods with the gold standard, indicating that both methods have a high diagnostic value.

Comparison of diagnostic efficacy of the combined diagnostic method. Table III provides the diagnostic efficacy of the three methods and the corresponding 95% CIs. It can be seen from the table that the diagnostic sensitivity of the combined method for postoperative metastases and recurrence was 93.43% (95% CI, 0.875-0.967), the specificity was 92.67% (95% CI, 0.856-0.965), the positive predictive value was 94.12% (95% CI, 0.884-0.972) and the negative predictive value was 91.81% (95% CI, 0.846-0.959). The values of these indicators were all higher than those for either PET/CT scan or serum SCC-Ag determination methods alone. The specificity and positive predictive values were subjected to the χ^2 test, and P-values were both below 0.05, indicating a significant difference. Two methods were compared at a time (PET-CT with combined method, SCC-Ag with combined method, respectively) by McNemar's χ^2 test or Pearson's chi-squared test. The statistical significance of these results is presented in Table III.

Comparison of ROC curve of the combined diagnostic method. The ROC curve was plotted using the results of the

Table IV. Comparison of receiver operating characteristic curve of the combined method for postoperative cervical cancer tumor recurrence and metastases.

				Asymptotic 95% CI	
Test variable	Area	Std. Error[a]	Asymptotic Sig.[b]	Lower bound	Upper bound
PET/CT diagnosis	0.878[c]	0.023	0.000	0.832	0.924
SCC-Ag diagnosis	0.819[c]	0.030	0.000	0.761	0.877
Combined method[d]	0.930	0.019	0.000	0.893	0.968

[a]Under the non-parametric assumption; [b]null hypothesis: true area=0.5; [c]P<0.05 vs. combined method; [d]the combined method has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

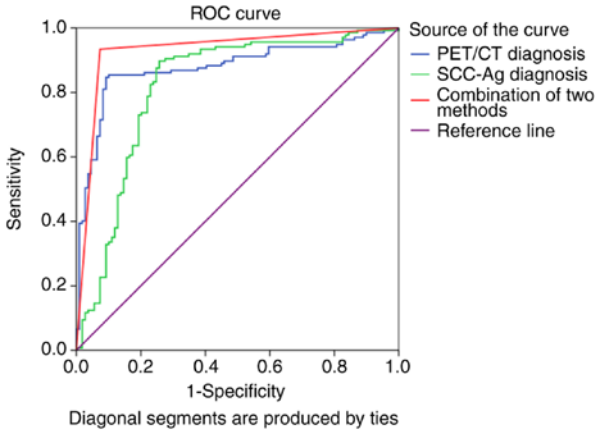

Figure 4. Comparison of ROC curve of the combination of two methods (PET/CT and SCC-Ag) for postoperative tumor recurrence and metastases. SCC-Ag, squamous cell carcinoma antigen; PET/CT, positron emission tomography/computed tomography; ROC, receiver operating characteristic.

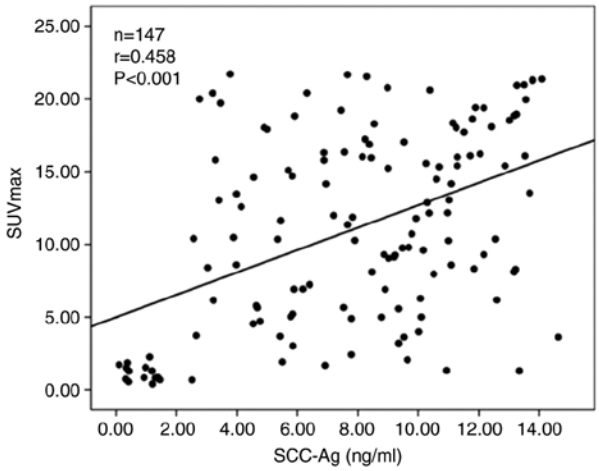

Figure 5. Scatter plot of the correlation between the average serum SCC-Ag level and SUV_{max}. SCC-Ag, squamous cell carcinoma antigen; SUV_{max}, maximum standardized uptake value.

gold standard pathology and follow-ups, and the area under the ROC curve was calculated. The area under the ROC curve for the combined method was 0.930±0.019 (95% CI, 0.893-0.968; P<0.001), which was larger than that for the PET/CT scan (0.878±0.023; 95% CI, 0.832-0.924; z-test value=2.07; P<0.05) and the SCC-Ag method (0.819±0.03; 95% CI, 0.761-0.877; z-test value=3.51; P<0.05). The results showed that the combined method had a higher diagnostic value for postoperative metastases and tumor recurrence in patients with CC (area under the ROC curve >0.9) (Fig. 4 and Table IV).

Correlation between SUV_{max} and serum SCC-Ag levels in patients with CC with postoperative metastases and tumor recurrence. The average SUV_{max} was 11.08±6.59 in 137 patients with CC with postoperative metastases and tumor recurrence, and the average serum SCC-Ag level was 6.84±5.43 ng/ml. The scatter plot of the association between the average serum SCC-Ag level and SUV_{max} was drawn for the 137 patients with CC with postoperative metastases and tumor recurrence (Fig. 5). The results showed that the serum SCC-Ag level was positively correlated with SUV_{max} (r=0.458; P<0.001), indicating that the higher the levels of serum SCC-Ag patients with metastasis and tumor recurrence are, the higher the SUV_{max} is.

Discussion

At present, the primary treatment for early stage CC is surgery, which may be combined with radiotherapy, chemotherapy, hyperthermia and gene therapy (20,21). The optimal individualized therapy should be developed based on the actual clinical situation of the patients. Approximately 80% of the recurrence cases occur within 2-3 years after the treatment for CC. Metastases largely occur in the pelvic and abdominal cavities (22,23). Tumor recurrence or metastases in gynecological malignancies are usually asymptomatic, making early discovery difficult, and there is still a lack of effective monitoring tools (24). Therefore, the diagnosis of CC recurrence and metastases by follow-up, use of tumor markers and imaging techniques is of high clinical significance. The clinical value of PET/CT scan with serum SCC-Ag in diagnosing postoperative metastases and recurrence in patients with CC was discussed in the current study.

^{18}F-FDG PET/CT is a fusing imaging technique that acquires morphological and functional images simultaneously. This technique can also show the position and scope of the lesions, and determine the presence of pelvic lymph node metastases and distant metastases (25). Due to these benefits, ^{18}F-FDG PET/CT has been increasingly used for the

diagnosis of CC recurrence and metastases. The present study further confirmed the clinical value of PET/CT in diagnosing CC recurrence and metastases. The area under the ROC curve was 0.878±0.023 (95% CI, 0.832-0.924; P<0.001), and the sensitivity and specificity of the PET/CT scan method were 84.67% (95% CI, 0.722-0.900) and 90.83% (95% CI, 0.834-0.953), respectively, which were consistent with other relevant studies (26-28).

Previous studies have shown that PET/CT has certain limitations in diagnosing CC recurrence and metastases (29,30): i) For lymph nodes <0.5 cm, PET/CT scan has limited diagnostic value; ii) ^{18}F-FDG is not specific for tumors and may produce false-positive results when diagnosing inflammatory lesions and lymph node micrometastases; iii) PET/CT images fail to recover the true activity in involved tissues once the volume of the disease is <2.5 times the spatial resolution of the scanner (31); and iv) given individual factors and variation of technical skills across the operators, SUV_{max} measurement is highly heterogenous. In the present study, missed diagnosis by PET/CT scan affected 21 patients with metastases and recurrence, with a missed diagnosis rate of 8.14%. This indicated a relatively low diagnostic sensitivity and failure to achieve an accurate result.

Serum SCC-Ag is the most widely used marker for residual CC recurrence and metastases after treatment (14,15). The serum SCC-Ag level is closely associated with the infiltration and metastases of squamous cell carcinoma of the cervix, and it is an independent risk factor of CC recurrence (30). The present study indicated that the area under the ROC curve for the serum SCC-Ag level method was 0.819±0.03 (95% CI, 0.761-0.877; P<0.001), and the sensitivity was also high 89.78% (0.831-0.941). Admittedly, the serum SCC-Ag level had a low specificity for diagnosing CC recurrence and metastases, which was only 74.31% (95% CI, 0.649-0.819). Moreover, the serum SCC-Ag determination alone is not able to indicate the location of tumor recurrence and metastases.

Previous studies highly recommend PET/CT as a routine imaging examination for patients with CC with a progressive increase in serum SCC-Ag levels for unknown reasons, and also for patients with negative serum SCC-Ag levels (32,33). The present study showed that the serum SCC-Ag level was positively correlated with SUV_{max} (r=0.458; P<0.001). Given the aforementioned benefits from both methods, PET/CT scan combined with serum SCC-Ag determination could be have a greater clinical value for diagnosing recurrence and metastases during the postoperative follow-up (34). The combined approach not only ensures a high sensitivity, but also a high specificity, reducing missed diagnosis and misdiagnosis, and providing more valuable information for the choice of appropriate salvage treatment for patients with recurrence. The diagnostic sensitivity of the combined method for postoperative metastases/recurrence in patients with early CC was 93.43% (95% CI, 0.875-0.967) and the specificity was 92.67% (95% CI, 0.856-0.965); the positive predictive value was 94.12% (95% CI, 0.884-0.972), the negative predictive value was 91.81% (95% CI, 0.846-0.959) and the area under the ROC curve was 0.930±0.019 (95% CI, 0.893-0.968; P<0.001). All of the aforementioned indicators for the combined method were significantly different from those using either PET/CT scan or serum SCC-Ag determination alone.

In view of the popularity and high cost of PET/CT, it is recommended that whole body PET-CT imaging should be performed as early as possible for the patients whose serum SCC Ag gradually increases during clinical follow-up, while other conventional imaging tests are negative.

There are a number of limitations to the present study. As a retrospective study, there may be a patient selection bias. The study was not stratified regarding the tumor stage and lymph node size, which may be confounding factors or represent bias. In the present study, a SUV_{max} of 2.5 as the standard threshold of tumor metastasis and recurrence, which is a truncated value. could have been affected by the differences in individual factors, such as the equipment utilized and the operator's technical level. Therefore, the diagnosis of this threshold is affected by a great heterogeneity and would require further quantification.

Taken together, for patients with early metaphase CC receiving treatment, PET/CT scan combined with serum SCC-Ag determination during the follow-up is capable of an earlier, more comprehensive and more accurate detection of recurrence/metastatic lesions. This combined diagnostic method is of high clinical application value to provide objective and valuable information for the development of subsequent treatment schemes.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YC conceived and designed the current study and contributed to writing the manuscript. CQ and SH performed the experiments. CQ and YC confirm the authenticity of all the raw data. LC, LZ and HD analyzed and interpreted the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved and monitored by the Ethics Committee of The Affiliated Hospital, Southwest Medical University (Luzhou, China). Written informed consent was provided by all the patients who participated in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Cohen PA, Jhingran A, Oaknin A and Denny L: Cervical cancer. Lancet 393: 169-182, 2019.
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I and Bray F (eds): Global cancer observatory: Cancer today. International Agency for Research on Cancer, Lyon, 2018.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
4. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ and He J: Cancer statistics in China, 2015. CA Cancer J Clin 66: 115-132, 2016.
5. Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105: 103-104, 2009.
6. Martins EB, Chojniak R, Kowalski LP, Nicolau UR, Lima EN and Bitencourt AG: Diffusion-weighted MRI in the assessment of early treatment response in patients with squamous-cell carcinoma of the head and neck: Comparison with morphological and PET/CT Findings. PLoS One 10: e0140009, 2015.
7. Harashavardhan NS, Naveen Kumar S, Uday Kumar NS, Ezhilarasi R and Bhavani B: A prospective analysis of magentic resonance imaging and computed tomography in staging with uterine cervix carcinoma: A single centre experience. J Chalmeda Anand Rao Institute Med Sci 16: 158-162, 2018.
8. Lee SI, Catalano OA and Dehdashti F: Evaluation of gynecologic cancer with MR imaging, 18F-FDG PET/CT, and PET/MR imaging. J Nucl Med 56: 436-443, 2015.
9. Gee MS, Atri M, Bandos AI, Mannel RS, Gold MA and Lee SI: Identification of distant metastatic disease in uterine cervical and endometrial cancers with FDG PET/CT: Analysis from the ACRIN 6671/GOG 0233 multicenter trial. Radiology 287: 176-184, 2018.
10. Dolgun ZN, Altintas AS, Ivan C and Balkanli P: Comparison of preoperative magnetic resonance imaging results with postoperative pathologic results in early stage uterine cervical cancer. Eur J Gynaecol Oncol 39: 935-938, 2018.
11. Herrera FG and Prior JO: The role of PET/CT in cervical cancer. Front Oncol 3: 34, 2013.
12. Ramlov A, Kroon PS, Jurgenliemk-Schulz IM, Leeuw AA, Gormsen LC, Fokdal LU, Tanderup K and Lindegaard JC: Impact of radiation dose and standardized uptake value of (18) FDG PET on nodal control in locally advanced cervical cancer. Acta Oncol 54: 1567-1573, 2015.
13. Selman TJ, Mann C, Zamora J, Appleyard TL and Khan K: Diagnostic accuracy of tests for lymph node status in primary cervical cancer: A systematic review and meta-analysis. CMAJ 178: 855-862, 2008.
14. Salvatici M, Achilarre MT, Sandri MT, Boveri S, Vanna Z and Landoni F: Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: Role in the early diagnosis of recurrence. Gynecol Oncol 142: 115-119, 2016.
15. Shimura K, Mabuchi S, Yokoi T, Sasano T, Sawada K, Hamasaki T and Kimura T: Utility of serum squamous cell carcinoma antigen levels at the time of recurrent cervical cancer diagnosis in determining the optimal treatment choice. J Gynecol Oncol 24: 321-329, 2013.
16. Fu J, Wang W, Wang Y, Liu C and Wang P: The role of squamous cell carcinoma antigen (SCC Ag) in outcome prediction after concurrent chemoradiotherapy and treatment decisions for patients with cervical cancer. Radiat Oncol 14: 146, 2019.
17. Choi KH, Lee SW, Yu M, Jeong S, Lee JW and Lee JH: Significance of elevated SCC-Ag level on tumor recurrence and patient survival in patients with squamous-cell carcinoma of uterine cervix following definitive chemoradiotherapy: A multi-institutional analysis. J Gynecol Oncol 30: e1, 2019.
18. Huang EY, Huang YJ, Chanchien CC, Lin H, Wang CJ, Sun LM, Tseng CW, Tsai CC, Ou YC, Fu HC, *et al*: Pretreatment carcinoembryonic antigen level is a risk factor for para-aortic lymph node recurrence in addition to squamous cell carcinoma antigen following definitive concurrent chemoradiotherapy for squamous cell carcinoma of the uterine cervix. Radiat Oncol 7: 13, 2012.
19. Kang S, Nam BH, Park JY, Seo SS, Ryu SY, Kim JW, Kim SC, Park SY and Nam JH: Risk assessment tool for distant recurrence after platinum-based concurrent chemoradiation in patients with locally advanced cervical cancer: A Korean gynecologic oncology group study. J Clin Oncol 30: 2369-2374, 2012.
20. Pieterse QD, Kenter GG, Maas CP, de Kroon CD, Creutzberg CL, Trimbos JB and Kuile MM: Self-reported sexual, bowel and bladder function in cervical cancer patients following different treatment modalities: Longitudinal prospective cohort study. Int J Gynecol Cancer 23: 1717-1725, 2013.
21. Jiao XB, Hu J and Zhu LR: The safety of ovarian preservation in early-stage adenocarcinoma compared with squamous cell carcinoma of uterine cervix: A systematic review and meta-analysis of observational studies. Int J Gynecol Cancer 26: 1510-1514, 2016.
22. Kim TH, Kim MH, Kim BJ, Park SI, Ryu SY and Cho CK: Prognostic importance of the site of recurrence in patients with metastatic recurrent cervical cancer. Int J Radiat Oncol Biol Phys 98: 1124-1131, 2017.
23. Bhatla N, Aoki D, Sharma DN and Sankaranarayanan R: Cancer of the cervix uteri. Int J Gynaecol Obstet 143 (Suppl 2): S22-S36, 2018.
24. Salani R, Khanna N, Frimer M, Bristow RE and Chen LM: An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of gynecologic oncology (SGO) recommendations. Gynecol Oncol 146: 3-10, 2017.
25. Yilmaz B, Dağ S, Ergul N and Çermik TF: The efficacy of pretreatment and after treatment 18F-FDG PET/CT metabolic parameters in patients with locally advanced squamous cell cervical cancer. Nucl Med Commun 40: 219-227, 2019.
26. Liu J, Yuan S, Wang L, Sun X, Hu X, Meng X and Yu J: Diagnostic and predictive value of using RGD PET/CT in patients with cancer: A systematic review and meta-analysis. Biomed Res Int 2019: 8534761, 2019.
27. Kitajima K, Suzuki K, Nakamoto Y, Onishi Y, Sakamoto S, Senda M, Kita M and Sugimura K: Low-dose non-enhanced CT versus full-dose contrast-enhanced CT in integrated PET/CT studies for the diagnosis of uterine cancer recurrence. Eur J Nucl Med Mol Imaging 37: 1490-1498, 2010.
28. Sironi S, Picchio M, Landoni C, Galimberti S, Signorelli M, Bettinardi V, Perego P, Mangioni C, Messa C and Fazio F: Post-therapy surveillance of patients with uterine cancers: Value of integrated FDG PET/CT in the detection of recurrence. Eur J Nucl Med Mol Imaging 34: 472-479, 2007.
29. Bentivegna E, Uzan C, Gouy S, Leboulleux S, Duvillard P, Lumbroso J, Haie-Meder C, Schlumberger M and Morice P: Correlation between [18f]fluorodeoxyglucose positron-emission tomography scan and histology of pelvic nodes in early-stage cervical cancer. Anticancer Res 30: 1029-1032, 2010.
30. Chou HH, Chang TC, Yen TC, Ng KW, Hsueh S, Ma SY, Chang CJ, Huang HJ, Chao A, Wu TI, *et al*: Low value of [18F]-fluoro-2-deoxy-D-glucose positron emission tomography in primary staging of early-stage cervical cancer before radical hysterectomy. J Clin Oncol 24: 123-128, 2006.
31. Driscoll DO, Halpenny D, Johnston C, Sheehy N and Keogan M: 18F-FDG-PET/CT is of limited value in primary staging of early stage cervical cancer. Abdom Imaging 40: 127-133, 2015.
32. Maffione AM, Piva M, Tsamita CS, Nanni C, Castellucci P, Ambrosini V, Lopci E, Musto A, Rampin L, Grassetto G, *et al*: Positron-emission tomography in gynaecologic malignancies. Arch Gynecol Obstet 280: 521-528, 2009.
33. Chong A, Ha JM, Jeong SY, Song HC, Min JJ, Bom HS and Choi HS: 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. Chonnam Med J 49: 20-26, 2013.
34. Pan L, Cheng J, Zhou M, Yao Z and Zhang Y: The SUVmax (maximum standardized uptake value for F-18 fluorodeoxyglucose) and serum squamous cell carcinoma antigen (SCC-ag) function as prognostic biomarkers in patients with primary cervical cancer. J Cancer Res Clin Oncol 138: 239-246, 2012.