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The value of ^{18}F-FDG PET/CT imaging combined with detection of CA125 and HE4 in the diagnosis of recurrence and metastasis of ovarian cancer

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Abstract. – OBJECTIVE: To explore the clinical application value of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging combined with detection of serum tumor molecular markers (carbohydrate antigen 125 (CA 125) and human epididymis protein 4 (HE4)) in the diagnosis of recurrence and metastasis of ovarian cancer.

PATIENTS AND METHODS: Clinical data about ^{18}F-FDG PET/CT imaging and serum CA125 and HE4 of 69 ovarian cancer patients after the first cytoreductive surgery and chemotherapy were retrospectively analyzed, and the clinical application value of ^{18}F-FDG PET/CT imaging combined with detection of CA125 and HE4 in the diagnosis of recurrence and metastasis of ovarian cancer was evaluated.

RESULTS: The ^{18}F-FDG PET/CT images of recurrence and metastasis of ovarian cancer showed hypermetabolism. The sensitivity, specificity, accuracy, predictive positive value, and predictive negative value of ^{18}F-FDG PET/CT imaging for the diagnosis of recurrence and metastasis of ovarian cancer were 90.74%, 86.67%, 89.86%, 96.08%, and 72.22%, respectively; those of CA125 for the diagnosis of them were 77.78%, 86.67%, 79.71%, 95.45% and 52.00%, respectively, and those of HE4 for the diagnosis of them were 70.37%, 93.33%, 76.84%, 97.44%, and 48.39% respectively. In addition, the sensitivity and specificity of ^{18}F-FDG PET/CT combined with detection of serum CA125 and HE4 for the diagnosis were 100.00% and 100.00%, respectively, significantly higher than those of separate ^{18}F-FDG PET/CT imaging, detection of serum CA125, and detection of serum HE4 (χ^2 = 5.243, 13.500, 18.783, p = 0.022, 0.000, 0.000; χ^2 = 4.000, 8.525, 9.864, p = 0.046, 0.004, 0.002), and the accuracy of the combination use of them was 95.65%, also significantly higher than that of separate CA125 and HE4 (χ^2 = 8.118, 10.315, p = 0.004, 0.001, both $p < 0.01$). Furthermore, the maximum standardized uptake value (SUVmax) of ^{18}F-FDG PET/CT imaging for recurrence and metastasis of ovarian cancer focuses was significantly positively correlated with serum CA125 and HE4 levels (r = 0.596, $p = 0.000$; r = 0.431, $p = 0.002$), and the serum CA125 level was also significantly positively correlated with serum HE4 level in patients with recurrent or metastasized ovarian cancer (r = 0.198, $p = 0.043$,).

CONCLUSIONS: ^{18}F-FDG PET/CT imaging combined with detection of serum CA125 and HE4 can significantly improve the diagnostic efficiency to recurrence and metastasis of ovarian cancer and is conducive to the early diagnosis of the recurrence and metastasis, which provides a basis for further clinical intervention.

Key Words:
Ovarian cancer, Recurrence and metastasis, PET, CA125, HE4, Joint detection.

Introduction

Epithelial ovarian cancer is one of the most common gynecologic malignant tumors, with incidence rate ranking third after corpus carcinoma and cervical cancer. Ovarian cancer has the highest mortality rate among gynecologic malignancies due to its insidious symptoms in the early stage and its characteristics that recurrence and metastasis are likely to occur after the first

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cytoreductive surgery and chemotherapy[1]. Seventy percent of ovarian cancer patients will suffer from recurrence and metastasis within 5 years[2,3], and the 5-year mortality of ovarian cancer patients is as high as 60-70%[4]. Therefore, finding recurrence and metastasis focuses in the early stage and taking corresponding effective treatment measures are the keys to lowering the mortality and improving the prognosis and quality of life of patients. Carbohydrate antigen 125 (CA 125) was once a classical marker for early diagnosis and evaluation of recurrence and metastasis of ovarian cancer, but single detection has low sensitivity and accuracy[5]. HE4 is a novel tumor molecular marker for the diagnosis of ovarian cancer, which has good application prospects in differentiating benign and malignant ovarian tumors and monitoring recurrence and metastasis[6]. However, serum tumor marker detection, as an *in vitro* diagnostic method, cannot accurately locate tumor recurrence and metastasis focuses, so it is impossible to judge secondary surgical indications. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging, as a new functional imaging technology, integrates structural imaging and functional metabolism[7], and the maximum standardized uptake value (SUVmax) of imaging agent ^{18}F-FDG can directly reflect the metabolic changes of tumor tissues and accurately locate recurrent and metastatic focuses. In this study, 69 ovarian cancer patients after the first cytoreductive surgery were enrolled as research participants, and the clinical application value of ^{18}F-FDG PET/CT imaging combined with detection of CA125 and HE4 in the diagnosis of recurrence and metastasis of ovarian cancer was retrospectively analyzed, with the goal of providing basis for early diagnosis of recurrence and metastasis of ovarian cancer after operation.

Patients and Methods

General Information

A total of 69 ovarian cancer patients suspected of tumor recurrence and metastasis after the first cytoreductive surgery and chemotherapy in our hospital from January 2014 to December 2016 were enrolled as research participants. Among them, according to histological type, there were 42 patients with ovarian serous adenocarcinoma, 18 patients with ovarian mucinous carcinoma, 3 patients with ovarian endometrioid carcinoma, 4 patients with mixed cystadenocarcinoma, and 2 patients with clear cell carcinoma. According to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging criteria, there were 10 patients in stage I, 13 patients in stage II, 39 patients in stage III, and 7 patients in stage IV. The research participants were between 35 and 81 years old, with an average age of (51.23±12.36) years. The histological classification of ovarian cancer is in accordance with the 2014 WHO (World Health Organization) classification standard for ovarian cancer. All patients underwent regular postoperative ^{18}F-FDG PET/CT imaging and serum CA125 and HE4 detection. Criteria for judging recurrence and metastasis: secondary postoperative pathological biopsy, puncture pathological biopsy, tumor cytology of pleural/peritoneal effusion or clinical follow-up data, with a follow-up time of 6-60 months. This investigation was approved by the Medical Ethics Committee of our hospital, and all research participants signed informed consent forms and participated in the study voluntarily.

^{18}F-FDG PET/CT Examination

The examination instrument of ^{18}F-FDG PET/CT applied in this study was GE Discovery 710 Clarity PET/CT, and ^{18}F-FDG was produced by the cyclotron of our center, with radiochemical purity larger than 95%. Examination methods: patients were asked to fast for solids and liquids for 4-6 hours before examination, and their blood glucose were controlled in the normal range of 3.11-6.61 mmol/L. Then, they were injected with imaging agent ^{18}F-FDG at 0.2 mCi/kg after 20 min of rest. Afterwards, they were asked to lay down for 60 min and then given PET/CT examination after bladder emptying. Firstly, CT plain scanning was performed to the whole body of each patient (from the top of skull to the upper thighs) under the following CT scanning parameters: current: 100 mA; voltage: 120KV, scanning slice thickness: 3.75 mm; reconstruction slice thickness: 1.5 mm. Subsequently, PET scanning was performed to the patient under the premise of keeping body position unchanged and breathing calm. Images were acquired in the 3D mode within the same CT scanning range, and the PET scanning was performed to the patient at each posture in the bed for 2 min, 6-7 postures in total. CT data were used to perform attenuation correction to PET images, and images were reconstructed using the inner iteration method. PET/CT fusion was completed automatically by computer system to obtain three-dimensional coronal, transverse, and sagittal images.

PET/CT Image Analysis

Two experienced doctors in the department of nuclear medicine were arranged to read the images independently and write their diagnosis report separately. If there were differences in diagnosis opinions, the differences were discussed, and then diagnosis opinions were obtained. Firstly, qualitative analysis and semi-quantitative analysis were carried out to visually inspect the uptake degree of the focus developer FDG. Then, the region of interest (ROI) was delineated for the visually positive focus area according to the location, size, and shape of the focus. The SUVmax was calculated using computer and the focus with SUVmax >2.5 was judged to be positive.

Examination of Serum Tumor Markers

Fasting venous blood (2 mL) was sampled from ovarian cancer patients after surgery, let stand, and centrifuged to take serum for later analysis. CA125 and HE4 were determined using the ELecsys-2010 electrochemical luminescence method with Roche original reagent in strict accordance with operation procedures and quality control meeting the requirements.

Statistical Analysis

In this study, data were statistically processed using SPSS 22.0 (IBM, Armonk, NY, USA). Measurement data were expressed as the mean ± standard deviation ($\bar{x}\pm s$), and comparison between groups was carried out using the independent-samples *t*-test. Comparison of enumeration data was carried out using the c^2-test. Pearson's correlation analysis was carried out to analyze the correlation, and Receiver operating characteristic (ROC) curves were drawn to obtain diagnostic indexes. $p<0.05$ indicates a significant difference.

Evaluation Indexes of Diagnostic Test

The standard method of diagnostic test evaluation was to statistically analyze positive and negative results of patients and non-patients (judged according to the gold standard) obtained using a certain test method, and then to calculate and obtain the diagnostic indexes commonly used in diagnostic tests. The test diagnosis results were divided into true positive (a), false positive (b), false negative (c), and true negative (d). The calculation formula: Sensitivity = a/(a+c); specificity = d/(d+b); accuracy = (a+d)/(a+b+c+d); predictive positive value = a/(a+b); predictive negative value = d/(d+c).

Results

Among the 69 research participants, there were 54 patients confirmed with recurrence and metastasis, and 15 patients without recurrence and metastasis according to secondary postoperative pathological biopsy, puncture pathological biopsy, tumor cytology of pleural/peritoneal effusion or clinical follow-up data.

^{18}F-FDG PET/CT Examination Results

According to ^{18}F-FDG PET/CT imaging diagnosis, among the 54 patients confirmed with recurrence and metastasis, there were 49 positive patients (true positive) and 5 negative patients (false negative), and among the 15 patients without recurrence and metastasis, there were 2 positive patients (false positive) and 13 negative patients (true negative) (Table I). The sensitivity and specificity of ^{18}F-FDG PET/CT in the diagnosis of recurrence and metastasis of ovarian cancer were 90.74% (49/54) and 86.67% (13/15), respectively.

The ^{18}F-FDG PET/CT images showed that the recurrence and metastasis focus of ovarian cancer was mainly located in the abdominal and pelvic cavity, indicating that abdominal and pelvic cavity is the main metastatic site of ovarian cancer. In addition, a total of 136 focuses were detected in the 49 positive patients, 103 of which were located in the abdominal and pelvic cavity (75.74%), 69 in soft tissue and intestinal tract, 22 in pelvic lymph nodes, 7 in the liver, 3 in the gastric wall, 1 in the spleen, and 1 in the adrenal. Additionally, it was found that there were 13 cervical and axillary lymph node metastases, 14 mediastinal lymph node metastases, 1 inguinal lymph node metastasis, 2 lymph node metastases in the lung and 3 lymph node metastases in the pleura. Of the 5 false negative cases, 9 metastatic focuses were found in the secondary operation, including 2 focuses in the peritoneum, 4 focuses in the pelvic lymph nodes, and 3

Table I. Comparison of 18F-FDG PET/CT imaging and pathological results.

Item	Pathology		Total
	Malignant	Benign	
18F-FDG PET/CT			
Malignant	49	3	52
Benign	5	12	17
Total	54	15	69

focuses in the abdominal lymph nodes. Of the 2 false positive patients diagnosed according to ^{18}F-FDG PET/CT imaging, their focuses all showed FDP metabolism increase in the colorectal or colon focuses, and they were confirmed to be inflammatory focuses according to endoscopic biopsy and pathology. The ^{18}F-FDG PET/CT images of ovarian cancer metastatic focus are shown in Figure 1.

Comparison of Diagnostic Value of Serum CA125 and HE4 for Postoperative Recurrence and Metastasis of Ovarian Cancer

The levels of serum CA125 and HE4 in the group with recurrence and metastasis after ovarian cancer surgery were significantly higher than those in the group without recurrence and metastasis after surgery (t = 4.172, p = 0.000, t

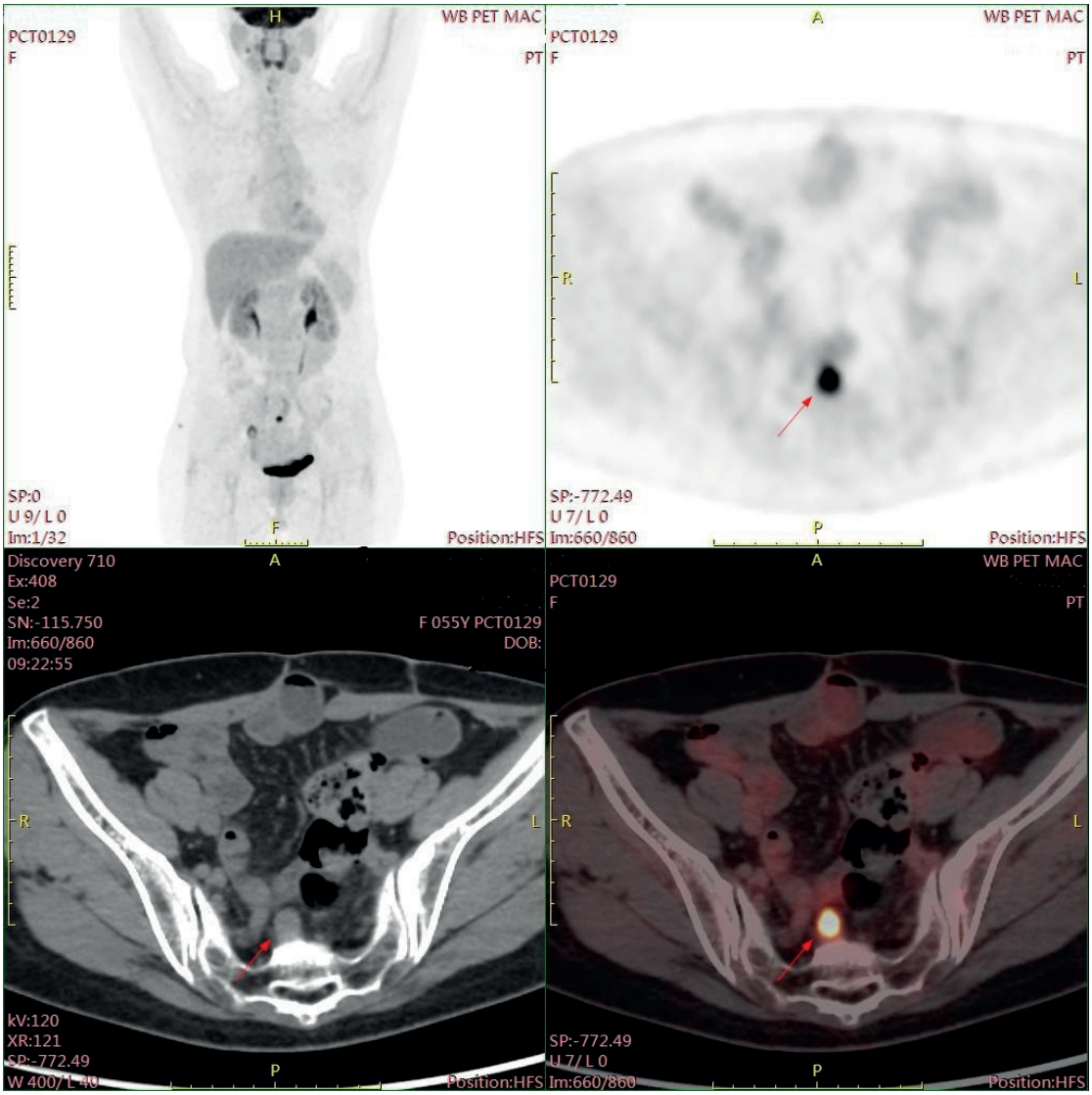

Figure 1. A 58 years old female patient undergoing 18F-FDG PET/CT imaging examination 2 years after ovarian cancer surgery. **A**, CT plain scan display (indicated by arrows): An increased soft tissue density of about 1.3*1.2 cm was seen in the anterior sacral region, with clear edges; **B**, PET/CT display (indicated by arrows): Increased radioactive uptake of the lesion, SUVmax approximately 9.7, the average SUV is about 5.5. The pathology of the second operation confirmed mesenteric lymph node metastasis of ovarian cancer. **C**, Plain CT scan (indicated by the arrow): In the right iliac vascular walking area, the size of about 2.0*1.6 cm soft tissue density increased shadow, with unclear edge. **D**, PET/CT display (indicated by arrows): the radioactive uptake of the lesion is increased, the SUVmax is about 6.1, and the average SUV is about 3.8. The pathology of the second operation confirmed mesenteric lymph node metastasis of ovarian cancer.

Table II. Comparison of serum CA125 and HE4 levels between the group with recurrence and metastasis after ovarian cancer surgery and the group without recurrence and metastasis after surgery ($\bar{x}\pm s$).

Group	n	CA125 (U/mL)	HE4 (*p*mol/ml)
The group with recurrence and metastasis	54	108.33±63.69[a]	218.89±74.77[a]
The group without recurrence and metastasis	15	39.55±18.85 *t*=4.172 *p*=0.000	118.27±44.49 *t*=4.957 *p*=0.000

Note: a indicates that in comparison with the group without recurrence and metastasis, $p<0.01$.

= 4.957, p = 0.000) (Table II). The ROC curves (Figures 2 and 3) showed that the ROC area-under-the-curves (AUCs) of CA125 and HE4 for the diagnosis of recurrence and metastasis of ovarian cancer were 0.847 and 0.858, respectively. CA125 and HE4 values corresponding to the maximum Youden index were selected as the critical values for judging recurrence and metastasis of ovarian cancer. The maximum Youden index of CA125 and HE4 was 0.644 and 0.637 respectively, and corresponding critical values were 57.50 U/L and 184.00 pmol/ml, respectively. Based on automatically convention, in the ROC curves, the sensitivity and specificity of CA125 in diagnosing recurrence and metastasis of ovarian cancer were 77.78% and 86.67%, respectively, and those of HE4 for it were 70.37% and 93.30%, respectively. In addition, the serum CA125 level in patients with recurrence and metastasis of ovarian cancer was significantly positively correlated with HE4 level in them (r = 0.198, p = 0.043).

Efficacy Comparison of Separate ^{18}F-FDG PET/CT Imaging, Detection of Serum CA125, Detection of Serum HE4, and Combination of Them in the Diagnosis of Recurrence and Metastasis of Ovarian Cancer

The sensitivity and negative predictive value of the combination of 18F-FDG PET/CT imaging, serum CA125, and HE4 in the diagnosis of ovarian cancer recurrence and metastasis were 100.00% and 100.00%, respectively, which were significantly improved compared with single tests (c^2 = 5.243 , 13.500, 18.783, p = 0.022, 0.000, 0.000), (c^2 = 4.000, 8.525, 9.864, p = 0.046, 0.004, 0.002), $p < 0.05$). The accuracy of ^{18}F-FDG PET/CT imaging combined with detection of serum CA125 and serum HE4 in diagnosing recurrence and metastasis of ovarian cancer was also significantly higher than that of separate detection of serum CA125 and serum HE4 (c^2 = 8.118, 10.315, p = 0.004, 0.001), but not significantly different

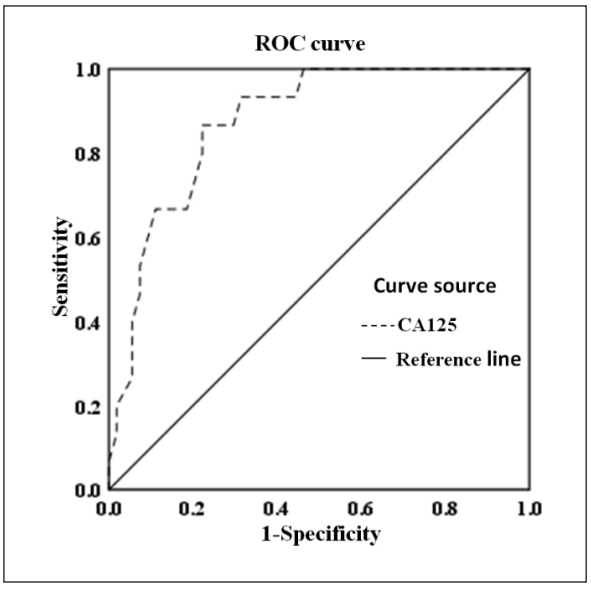

Figure 2. ROC curve of serum CA125 in the diagnosis of recurrence and metastasis of ovarian cancer.

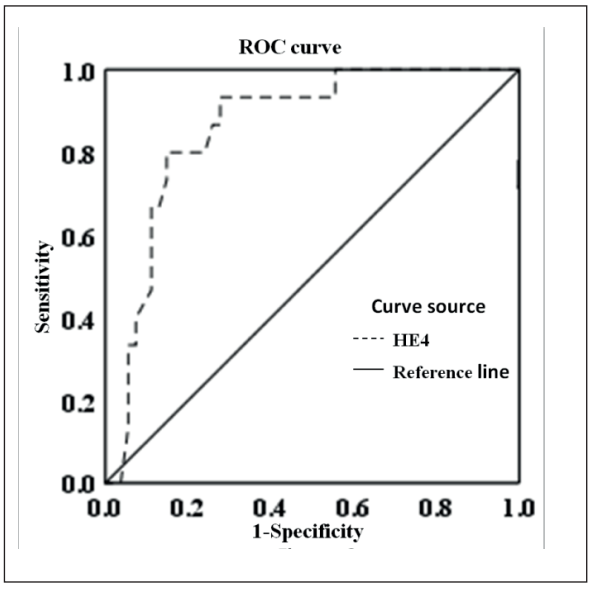

Figure 3. ROC curve of serum HE4 in the diagnosis of recurrence and metastasis of ovarian cancer.

Table III. Efficacy comparison of separate ^{18}F-FDG PET/CT imaging, detection of serum CA125, detection of serum HE4, and combination use of them in the diagnosis of recurrence and metastasis of ovarian cancer (%).

Detection indexes	Sensitivity	Specificity	Accuracy	Predictive positive value	Predictive negative value
^{18}F-FDG PET/CT	90.74 (49/54)	86.67 (13/15)	89.86 (62/69)	96.08 (49/51)	72.22 (13/18)
CA125	77.78 (42/54)	86.67 (13/15)	79.71 (55/69)	95.45 (42/44)	52.00 (13/25)
HE4	70.37 (38/54)	93.33 (14/15)	76.81 (53/69)	97.44 (38/39)	48.39 (15/31)
Combination of the three	100.00 (54/54)b	80.00 (12/15)	95.65 (66/69)c	94.74 (54/57)	100.00 (12/12)[b]

Note: bindicates that in comparison with separate one, $p<0.05$, and cindicates that in comparison with separate detection of CA125 and HE4, $p<0.05$.

from that of ^{18}F-FDG PET/CT imaging alone ($c^2 = 1.725$, $p = 0.189$). In addition, the negative value predicted by ^{18}F-FDG PET/CT imaging combined with detection of serum CA125 and serum HE4 was significantly higher than that predicted by separate use of them ($c^2 = 4.000, 8.525, 9.864$; $p = 0.046, 0.004, 0.002$) (Table III).

Discussion

Due to the high recurrence rate and high metastasis rate of ovarian cancer after operation, even if there is no visible residual focus after the first tumor reductive surgery and standard postoperative chemotherapy has been applied, a considerable number of patients will still suffer from recurrence and metastasis after initial treatment[8]. Therefore, finding postoperative residual focuses, recurrent focuses, and metastatic focuses as soon as possible is of great significance for guiding secondary surgery and subsequent chemotherapy to improve the survival of patients[9-12]. It is difficult to accurately find recurrence and metastasis focuses in the early stage with color Doppler ultrasound, CT, and MRI, and medical scholars have been consistently exploring measures to find them in the early stage.

^{18}F-FDG PET/CT, as a new imaging technology, integrates PET and CT and fully combines the anatomical structure of tissues with the metabolic function of cells, thus realizing organic combination of anatomical imaging and functional imaging[13]. Tumor cells need energy for growth, and the source of energy is glucose. The structure of FDG is similar to that of glucose. When ^{18}F-FDG is injected intravenously, FDG is absorbed by tumor cells in recurrence and metastasis focuses, but cannot be metabolized into carbon dioxide (CO_2) and water (H_2O), so it is stored in tumor cells in the focuses, and then it is imaged by isotope fluorine-18[14], which not only can accurately locate the focuses, but also can accurately find early tumor metastasis through the metabolic changes of tumor cells, especially soft tissue shadows that cannot be qualitatively determined by color Doppler ultrasound and sites that are not easy to find[15-17]. Therefore, ^{18}F-FDG PET/CT imaging plays an important role in the early diagnosis and treatment of recurrence and metastasis of ovarian cancer. ^{18}F-FDG PET/CT is noninvasive, sensitive, and can be used to obtain whole-body localization images with one injection of contrast agent. It uses the difference between the SUVmax of tumor focus contrast agent FDG and normal tissues and benign focuses to achieve the purpose of differentiating benign from malignant. It has been widely used in the diagnosis and treatment of recurrence and metastasis of ovarian cancer[18,19]. The results of this study showed that the abdominal and pelvic cavity was the main metastatic site of ovarian cancer, and ^{18}F-FDG PET/CT had a sensitivity of 90.74% in diagnosing recurrence and metastasis of ovarian cancer, which is basically consistent with the sensitivity of 92.2% reported by Rusu et al[20]. ^{18}F-FDG PET/CT imaging can reflect false positive due to the influences of inflammation and other factors, and the uptake of contrast agent FDG in inflammatory focuses is higher than that of normal tissues, so image analysis should be based on compressive clinical analysis[21-23].

Serum tumor marker detection, a commonly used inspection method for malignant tumor diagnosis and prognostic follow-up, is simple to operate at low costs, and the samples are easy to be collected. CA125 is the most widely used classical serum tumor marker in clinical diagnosis of ovarian cancer at present. It has high expression in epithelial ovarian cancer tissues[24], and it is of great significance in the early diagnosis of ovari-

an cancer and, more importantly, in the diagnosis of recurrence and metastasis of ovarian cancer after initial treatment. Therefore, dynamic detection of serum CA125 level can be used for monitoring of efficacy on ovarian cancer and the severity of ovarian cancer and judgment of prognosis of the cancer[25-27]. In this study, according to the ROC curve analysis, if the diagnostic threshold of serum CA125 was set as 35.00 U/L according to the conventional standard, the sensitivity and specificity of it were 88.90% and 66.70%, respectively. Although the sensitivity is high, the specificity is too low. If the diagnostic threshold of serum CA125 was set as 57.50 U/L, the sensitivity and specificity of it were 77.78% and 86.67%, respectively. Although the sensitivity decreased, the diagnostic specificity was improved and the false positive was reduced, suggesting that 57.50 U/L can be used as the diagnostic threshold for CA125 to diagnose recurrence and metastasis of ovarian cancer.

HE4, as a new tumor molecular marker, has been recognized in the diagnosis of ovarian cancer[28]. In the process of malignant transformation of ovarian tissue cells, the HE4 level in peripheral blood significantly increases due to gene mutation, abnormal gene transcription regulation and continuous transcription and translation of HE4 gene[29]. Moore et al[30] found that the expression of serum HE4 in ovarian cancer patients is significantly correlated with that of serum CA125 in the patients, and joint detection of them is complementary, and other studies have reported that if the serum HE4 level in ovarian cancer patients cannot return to normal after cytoreductive surgery for ovary tumors and chemotherapy, the prognosis is poor and there is a possibility of recurrence and metastasis, and such patients should be followed up in a short period of time[31,32]. Therefore, serum HE4 is a relatively good indicator for diagnosing recurrence and metastasis of ovarian cancer. In this study, according to ROC curves, when the judgment threshold of HE4 was 184.00 pmol/mL, the sensitivity and specificity of it in diagnosing recurrence and metastasis of ovarian cancer were 70.37% and 93.33%, respectively. Although the specificity is high, the sensitivity is low, so it is necessary to combine HE4 with other indexes to improve the efficiency of HE4.

In summary, in view of the easy recurrence and metastasis of ovarian cancer after surgery, follow-up monitoring should be followed closely. The results of this study show that ^{18}F-FDG PET/CT imaging combined with serum CA125 and HE4 tests for diagnosing recurrence and metastasis of ovarian cancer has significantly improved sensitivity, accuracy, and negative predictive value compared with individual tests. The novelty of this study is that ^{18}F-FDG PET/CT imaging combined with serum CA125 and HE4 tests can complement each other and confirm each other, which can significantly improve the diagnostic efficacy of ovarian cancer recurrence and metastasis.

Conclusions

The novelty of this study is that ^{18}F-FDG PET/CT imaging combined with serum CA125 and HE4 tests can complement each other and confirm each other, which can significantly improve the diagnostic efficacy of ovarian cancer recurrence and metastasis and provide reference for the early diagnosis of ovarian cancer recurrence and metastasis. The sample size of this study is limited. In the future, more samples will be included, and the clinical values of combined detection will be explained.

Conflict of Interests

The authors declare that they have no conflict of interests.

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