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The maximum standardized uptake value and extent of peritoneal involvement may predict the prognosis of patients with recurrent ovarian cancer after primary treatment

A retrospective clinical study

Yuanyuan Jiang, MD[a,b], Guozhu Hou, MD[a,b], Fengyu Wu, MD[c], Zhaohui Zhu, MD[a,b], Wei Zhang, MD[d,*], Wuying Cheng, MD[a,b,*]

Abstract

We investigated the effect of the maximum standardized uptake value (SUV_{max}) and peritoneal dissemination derived from ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) imaging on prognosis in patients with recurrent ovarian cancer.

We retrospectively analyzed 145 patients with suspected recurrent ovarian cancer who had undergone ^{18}F-FDG PET/CT scans after cytoreductive surgery and chemotherapy. The degree of peritoneal spread was classified as localized (1–3 FDG foci) or diffuse (>3 FDG foci). Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off values for predicting recurrence.

A total of 145 patients were retrospectively reviewed in this study. 29 patients were excluded as their follow-up results were not available. One hundred sixteen patients were included in the final analysis. The median duration of progression-free survival was 14 months. ^{18}F-FDG PET/CT detected peritoneal carcinomatosis in 82 patients. With a cut-off SUV_{max} of 2.0 obtained from the ROC curve analysis, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of SUV_{max} of peritoneal carcinomatosis for predicting recurrence were 77.6%, 87.5%, 65.1%, 97.4%, and 38.9%, respectively. The area under the curve was 0.85. In a multivariate analysis, significant independent prognostic variables were SUV_{max} of peritoneal disease, peritoneal dissemination, and CA125 levels. In patients with peritoneal involvement, the Kaplan-Meier survival curves showed significantly longer PFS in those with localized disease.

SUV_{max} of peritoneal disease is valuable in predicting the recurrence of ovarian cancer. SUV_{max} of peritoneal disease, peritoneal dissemination and CA125 level could be used as independent prognostic factors for ovarian cancer patients.

Abbreviations: ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, AUC = area under the curve, CI = confidence intervals, CT = computed tomography, FIGO = International Federation of Gynecology and Obstetrics, HR = Hazard ratios, MRI = Magnetic Resonance Imaging, OSEM = ordered-subset expectation-maximization, PET = positron emission tomography, PFS = progression-free survival, ROC = Receiver operating characteristic, ROC = Receiver operating characteristic, ROIs = regions of interest, SUV_{max} = Maximum standardized uptake value, WHO = World Health Organization.

Keywords: ovarian cancer, peritoneal involvement, PET/CT, prognosis, SUV_{max}

Editor: Shizhang Ling.

YJ and GH contributed equally to this work.

Ethical approval was waived by the Ethics Committee of our hospital because this is a retrospective study.

This work is supported by the National Natural Science Foundation of China (no. 81371588, no.81101074).

The authors report no conflicts of interest.

[a] Department of Nuclear Medicine, Peking Union Medical College Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, [b] Beijing Key Laboratory of Molecular Targeted Diagnosis and Therapy in Nuclear Medicine, Beijing, [c] Department of PET/CT Centre, the Affiliated Hospital of Qingdao University, Qingdao, [d] Department of Nuclear Medicine, Affiliated Hospital of Southwest Medical University, Lu Zhou, Sichuan, China.

[*] Correspondence: Wuying Cheng, MD, Department of Nuclear Medicine, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Wangfujing, Dongcheng District, Beijing 100730, China (e-mail: cwypumch@126.com), Wei Zhang, MD, Department of Nuclear Medicine, Affiliated Hospital of Southwest Medical University, Lu Zhou, Sichuan, China (e-mail: zhangwscd@163.com).

How to cite this article: Jiang Y, Hou G, Wu F, Zhu Z, Zhang W, Cheng W. The maximum standardized uptake value and extent of peritoneal involvement may predict the prognosis of patients with recurrent ovarian cancer after primary treatment: A retrospective clinical study. Medicine 2020;99:8(e19228).

Received: 28 September 2019 / Received in final form: 17 January 2020 / Accepted: 21 January 2020

http://dx.doi.org/10.1097/MD.0000000000019228

1. Introduction

Ovarian cancer is the most commonly diagnosed gynecologic malignancy and the leading cause of cancer-related deaths in women.[1] The symptoms of ovarian cancer are nonspecific, and most cases are detected at advanced stages. Standard treatment of advanced ovarian cancer includes aggressive cytoreductive surgery followed by chemotherapy. Approximately 20% to 30% of patients with early-stage disease and 50% to 75% of patients with late-stage disease tend to recur despite adequate primary therapy. Metastases usually occur as a result of peritoneal, lymphangitic, or hematogenous spread of the tumor, with the peritoneal route being the most common.[2]

The clinical follow-up generally includes measurement of the serum cancer antigen CA125, physical examination, and imaging examinations. Serum CA125 is elevated in more than 90% of patients with late-stage disease, but is nonspecific, as normal levels cannot be reliable to exclude recurrence, and elevated values cannot differentiate between localized and diffuse tumor recurrence. Computed tomography (CT), Magnetic Resonance Imaging (MRI), and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT are the most commonly used imaging modalities in patients with suspected recurrent ovarian cancer.[3] However, small peritoneal deposits are difficult to detect with CT and MRI because of the anatomical changes due to treatment and field of view limitations. ^{18}F-FDG PET/CT helps in detecting these foci, especially in cases where CA125 levels are rising, but conventional imaging studies show negative or equivocal findings.[4] Metabolic characterization of ovarian cancer by PET/CT has resulted in reports of several potential prognostic factors.[5–8] However, most were reported in a pre-treatment stage, with limited data available about the post-treatment stage. We hypothesized that tumor metabolic parameters might be useful as prognostic markers that may predict recurrence or progression-free survival (PFS).

2. Materials and methods

2.1. Patients

A retrospective analysis of 145 patients suspected of recurrent ovarian cancer was performed. Inclusion criteria were as follows:

(1) the patients suspected of recurrent ovarian cancer due to clinical symptoms or elevated CA125 levels;
(2) the CT or MRI results before the PET/CT scan were negative or equivocal;
(3) the primary tumor was removed by surgery before the PET/CT scan.

All patients underwent ^{18}F-FDG PET/CT scans for further evaluation. Follow-up results were confirmed at pathologic examination after exploratory surgery or further information from clinical follow-up (positive findings in vaginal and/or abdominal ultrasound, further increase in tumor marker levels without therapy, a morphologic response to chemotherapy or a decrease in the patients' clinical condition). Twenty-nine patients were excluded from the final analysis because follow-up data after the scan were not available. The degree of peritoneal spread was classified as localized (1–3 focal sites of ^{18}F-FDG uptake) or diffuse (more than 3 sites of ^{18}F-FDG uptakes). Stage was confirmed according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. The histological cell types were classified according to the World Health Organization (WHO) classification.[9]

2.2. PET/CT technique and image analysis

All patients fasted for at least 4 hours before PET/CT acquisition. Serum glucose levels measured at the time of ^{18}F-FDG injections were less than 150 mg/dL in all patients. A PET/CT scan consisted of five-bed positions with 2 minutes per table position from the skull base to the femoral region 60 minutes after intravenous injection of 5.55 MBq/kg body weight ^{18}F-FDG was performed. PET data were acquired in three-dimensional mode. CT was performed before the PET, and the resulting data were used to generate an attenuation correction map. Images were reconstructed using an ordered-subset expectation-maximization (OSEM) iterative reconstruction algorithm. The CT acquisition parameters were as follows: 140 kV, 120 mAs, and slice thickness 5 mm.

Semi-quantitative analysis of the data was performed. The maximum standardized uptake value (SUV_{max}) for each suspicious lesion was measured. Either lymph node uptake or widespread peritoneal uptake greater than that in the liver or surrounding tissue was considered to be suspicious of metastatic/peritoneal dissemination. For the measurement of FDG uptake, regions of interest (ROIs) were manually placed on the main lesion and suspected metastasis. Images were evaluated by two nuclear medicine physicians who were informed about the clinical data of the patient at the time of the scan.

2.3. Statistical analysis

Receiver operating characteristic (ROC) analysis was performed to determine a cut-off value for SUV_{max} of peritoneal disease to predict ovarian cancer recurrence. The area under the curve was calculated with ROC analysis. The PFS was defined as the time from the PET/CT scan to the appearance of clinical or radiological progression. The differences in PFS were assessed by Kaplan–Meier curves. Multivariate analyses using the Cox proportional hazards regression model were performed to assess the potential independent effects of multiple factors on PFS (age, stage, pathological type, CA125 levels, lymph node involvement, peritoneal dissemination, and extra-abdominal disease). Hazard ratios (HR) with 95% confidence intervals (CI) were computed. All analyses were performed with commercial software (IBM SPSS Statistics version 21, IBM Corp., Somers, NY). A $P < .05$ was considered to indicate a significant difference.

3. Results

3.1. Patients

A total of 145 patients were retrospectively reviewed in this study. Twenty-nine patients were excluded as their follow-up results were not available. One hundred sixteen patients were included in the final analysis. Basic data of the final 116 patients are listed in Table 1.

3.2. The prognostic value of SUV_{max} of peritoneal disease

82/116 (71%) patients were found with peritoneal carcinomatosis on ^{18}F-FDG PET/CT. The SUV_{max} of the peritoneal carcinomatosis ranged from 0.9 to 19.9. With a SUV_{max} cut-off value of 2.0 obtained from the ROC curve analysis, the sensitivity, specificity,

Table 1

Patient characteristics for recurrent ovarian cancer.

Characteristics	Values
Total number of patients	116
Median age (range)	52 (35–81 years)
FIGO stage, n (%)	
I	3 (2.6)
II	3 (2.6)
III	105 (90.5)
IV	5 (4.3)
Histology, n (%)	
Serous	77 (66.4)
Clear cell	11 (9.5)
Endometrioid	9 (7.8)
Mixed type	6 (5.2)
Other	13 (11.2)
CA-125, median (range)	118.5 (5–1576 U/ml)
Median duration of PFS (range)	14 (1–53 months)
Number of PET/CT scan, n (%)	
1	21 (18.1)
2	55 (47.4)
>3	40 (34.5)

FIGO = International Federation of Gynecology and Obstetrics; PET/CT = positron emission tomography/computed tomography; PFS = progression-free survival.

accuracy, positive predictive value, and negative predictive value of SUV_{max} of peritoneal disease for predicting ovarian cancer recurrence were 77.6%, 87.5%, 65.1%, 97.4%, and 38.9%, respectively. The area under the curve (AUC) was 0.85. Readers' ROC curves are shown in Figure 1.

3.3. Correlation of the extent of peritoneal disease with PFS

Of the 116 patients enrolled, 82 patients were found with peritoneal disease and 34 patients without the peritoneal disease. A Kaplan-Meier survival curve performed between these 2 groups showed patients without peritoneal disease had a significantly longer PFS (Fig. 2). Eighty-two patients with peritoneal disease were further classified into 2 groups by the degree of peritoneal involvement: 62 patients with localized disease, 20 patients with diffuse disease. A Kaplan-Meier survival curve among these 3 groups (patients without peritoneal disease, patients with localized peritoneal disease and those with diffuse peritoneal disease) was performed and showed a significant difference in PFS (Fig. 3). Of the 82 patients with peritoneal disease, ^{18}F-FDG PET/CT also showed extra-abdominal involvement in 24 patients. But There was no difference in survival between patients with disease confined to the peritoneum and those who also had extraperitoneal metastases ($P = .764$).

3.4. Multivariate analysis

The Cox proportional hazard model was used to evaluate the prognostic value of parameters including age, stage, pathological

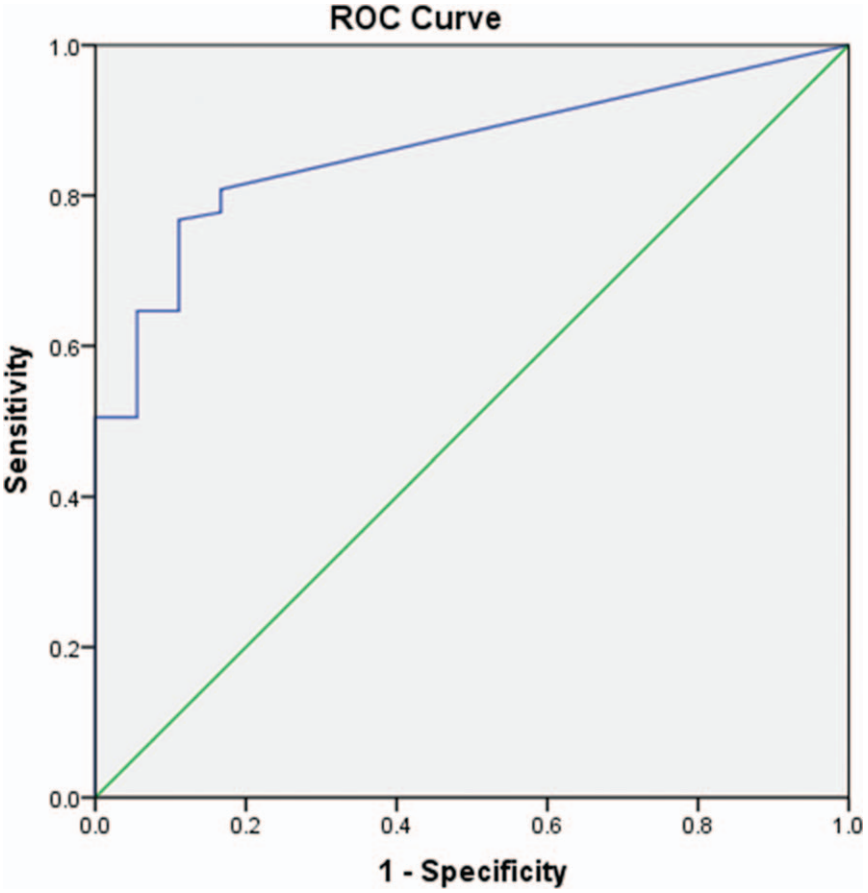

Figure 1. ROC curve analysis for determination of the cut-off value of SUV_{max} of peritoneal disease for predicting recurrence. The area under the curve is 0.85.

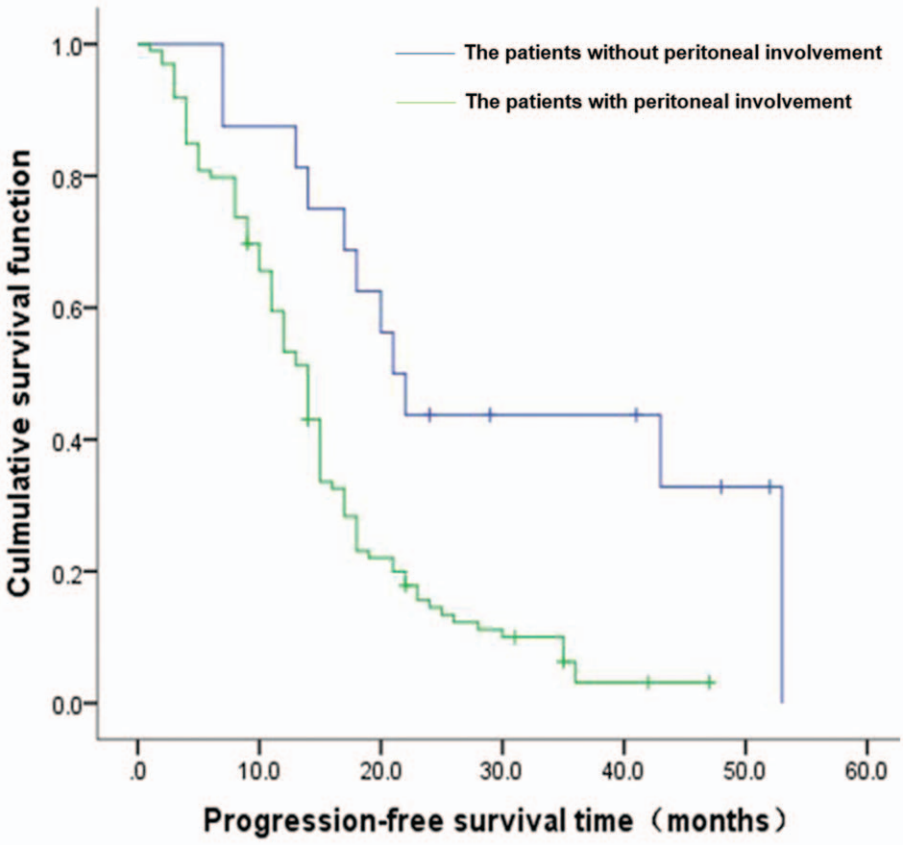

Figure 2. PFS among patients with or without peritoneal involvement. The green line represents the patients with peritoneal involvement, and the blue line represents patients without peritoneal involvement. The Kaplan-Meier survival plot shows a significant difference in PFS between these 2 groups: ($P = .026$; HR, 1.06).

type, CA125 levels, lymph node involvement, peritoneal dissemination, and extra-abdominal disease. In a multivariate analysis, only the SUV_{max} of peritoneal carcinomatosis ($P = .026$, HR 1.06,95% CI, 1.007–1.116), peritoneal dissemination ($P < .05$; HR, 1.354; 95% CI, 1.001–1.832) and CA125 levels ($P = .04$; HR, 1.001; 95% CI, 1.000–1.002) were found to be significant independent prognostic variables.

4. Discussion

Imaging modalities visualizing metabolic pathways provide an opportunity to monitor the metabolism of tumors in vivo and evaluate the response to therapy.[10]^{18}F-FDG PET/ CT has been investigated in patients with ovarian cancer, displaying high diagnostic accuracy of post-treatment recurrence that results in a change of patient management, especially in subjects with elevated CA125 and negative results of other imaging techniques.[11,12] Extensive data have shown that ^{18}F-FDG is valuable in determining prognosis of preoperative ovarian cancer.[13,14] However, there are relatively fewer studies in terms of PET/CT's utility in predicting prognosis of recurrent ovarian cancer. In this study, we assessed the association between the post-treatment values of SUV_{max} of peritoneal carcinomatosis, the extent of peritoneal involvement, CA125 levels, and the outcomes of ovarian cancer.

Ovarian cancer can spread locally within the pelvis with subsequent spread within the peritoneal cavity to the rest of the abdomen. In patients with peritoneal metastases, PET/CT demonstrates high sensitivity and accuracy in detecting lesions compared with CT and MRI.[15,16] SUV_{max}-based assessment of response has been found to be one of the most common predictors of recurrent disease after primary treatment.[17,18] The presence of abnormal peritoneal FDG uptake has been widely accepted as a criterion for differentiation between benign and malignant disease in ovarian cancer. A high SUV_{max} has been shown to correlate with tumor proliferation and other signs of aggressive tumor behavior and portends worsened survival in these patients. We found that SUV_{max}, plus peritoneal dissemination, are important prognostic factors. In a retrospective study testing the prognostic value of the ^{18}F-FDG PET/CT parameters (SUV_{max}, metabolic tumor volume, and total lesion glycolysis) at the time of the first relapse of ovarian cancer, Perrone et al found that only SUV_{max} demonstrated to be significantly associated to survival and represented a prognostic factor.[19] Another retrospective study by Sala et al[20] also found that higher SUV_{max} values of peritoneal deposits in patients with recurrent ovarian cancer were significantly associated with poor survival and may have potential as prognostic biomarkers for patients with recurrent ovarian cancer.

In this study, we found that peritoneal dissemination and extra-abdominal involvement could be used to predict the patients' PFS. Patients without peritoneal disease had a significantly longer PFS than those with peritoneal disease. And a significant difference in PFS was also found between

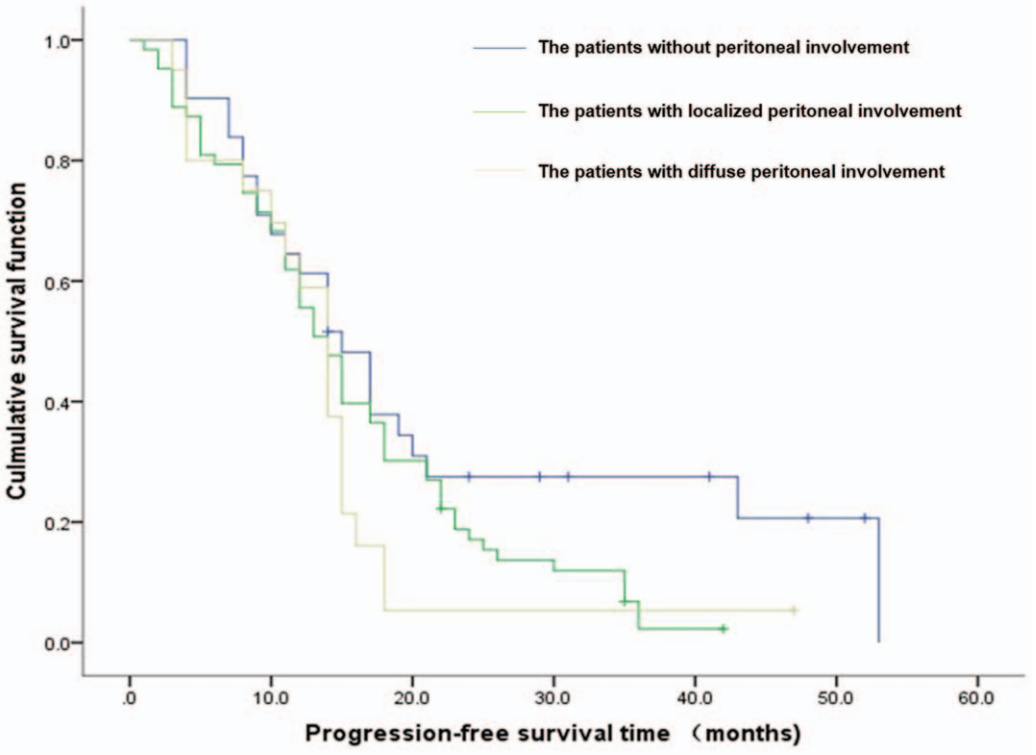

Figure 3. PFS among patients with ovarian cancer stratified by the degree of peritoneal involvement. Kaplan-Meier survival plot shows a significant difference in PFS among the groups: The blue line represents patients without the peritoneal disease. The green line represents the localized peritoneal involvement. The yellow line represents the diffuse peritoneal carcinomatosis. ($P < .05$; HR, 1.354).

patients with localized peritoneal disease and those with diffuse peritoneal disease. Our findings are in line with Hebel et al,[21] who demonstrated that there was a significantly better survival in FDG-PET/CT negative than in positive patients, and no difference in survival between patients who only had metastases confined to the peritoneum on FDG PET/CT and those who also had extra-abdominal involvement.

CA125 is currently the most widely used tumor marker for initial diagnosis and monitoring of response to chemotherapy for ovarian cancer. Several studies have documented that an elevation of serum CA125 can precede the appearance of clinically or radiographically measurable recurrence.[6,8,22,23] 56.9% of patients enrolled in this study had elevated CA125 levels, and CA125 level was also found to be an independent predictor of PFS in a multivariate model. However, increased CA125 values cannot provide information about the locations of tumor recurrence or differentiate between localized and diffuse tumor recurrence.[13,14] Furthermore, 20% of ovarian cancers have little or no expression of CA125.[9] In our study, ^{18}F-FDG PET/CT showed peritoneal dissemination in 8 patients with normal CA125.

Of course, the present study has its limitations due to the retrospective design. The treatment patients received varied highly, and the duration of follow-up and survival was relatively short.

In conclusion, the SUV_{max} of peritoneal disease is valuable in predicting the recurrence of ovarian cancer. SUV_{max} of peritoneal disease, peritoneal dissemination and CA125 levels could be used as independent prognostic factors for ovarian cancer patients.

Author contributions

Funding acquisition: Wuying Cheng.
Investigation: Wei Zhang, Fengyu Wu.
Methodology: Zhaohui Zhu.
Project administration: Wuying Cheng, Wei Zhang.
Writing – original draft: Yuanyuan Jiang, Guozhu Hou.
Writing – review & editing: Yuanyuan Jiang, Guozhu Hou.

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