Identification of Metabolic Biomarkers Using Serial ^{18}F–FDG PET/CT for Prediction of Recurrence in Advanced Epithelial Ovarian Cancer

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Abstract

PURPOSE. To evaluate the prognostic value of metabolic parameters derived from serial ^{18}F fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in patients with advanced epithelial ovarian cancer (EOC). *METHODS*. Thirteen patients with advanced EOC who received surgical staging and adjuvant platinum-based combination chemotherapy were prospectively enrolled. ^{18}F–FDG PET/CT was performed before and after the surgical staging, and after third cycle of chemotherapy. Tumor glucose metabolism at baseline and its change after operation and third cycle of chemotherapy such as changes of maximum standardized uptake values (ΔSUV_{max}) via ^{18}F–FDG PET/CT were measured, and assessed regarding their ability to predict recurrence. *RESULTS*. Median duration of progression-free survival (PFS) was 25 months (range, 13–34), and although optimal debulking was performed in 10 patients, 5 (38.5%) patients experienced recurrence. Univariate analyses showed significant associations between recurrence and low ΔSUV_{max} after surgical staging, and low SUV_{max} change after third cycle of chemotherapy. Multivariate analysis identified low ΔSUV_{max} after third cycle of chemotherapy as an independent risk factor for recurrence ($P = .047$, hazard ratio (HR) 16.375, 95% CI 1.041–257.536). Kaplan–Meier survival curves showed that PFS significantly differed in groups categorized based on ΔSUV_{max} after chemotherapy ($P = .001$, log-rank test). *CONCLUSIONS*. ^{18}F–FDG PET/CT allows for prediction of treatment response by the level of FDG uptake in terms of SUV at baseline and after chemotherapy. The metabolic response measured as ΔSUV_{max} after third cycle of chemotherapy appears to be promising predictor of recurrence in patients with advanced EOC.

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Introduction

The majority of epithelial ovarian cancer (EOC) patients present with advanced stages of disease and tumor spread in the abdominal cavity [1]. Standard treatment of EOC includes aggressive cytoreductive surgery followed by platinum/taxane-based chemotherapy [2]. Surgical cytoreduction increases the efficacy of additional adjuvant therapy, and accomplishment of optimal cytoreduction is reported to be critical for better prognosis [3].

Imaging metabolic pathways offers an alternative to visualize therapeutic effects. Malignant transformation of cells is frequently associated with increased metabolic activity. Positron emission tomography/computed tomography (PET/CT) using ^{18}F fluorodeoxyglucose (FDG) has

been successfully employed to visualize enhanced glucose utilization in tumor tissue.

Several studies have shown that changes in tumor metabolism occur early in the course of therapy and precede the reduction of tumor size [4–6]. These studies suggest that quantification of tumor glucose metabolism is highly accurate for monitoring effects of chemotherapy. In breast cancer, sequential FDG-PET imaging provided a sensitive means of early detection of response to therapy [7,8]. Previous reports demonstrated the clinical use of PET/CT in advanced EOC in neoadjuvant setting [9–11].

However, no information is currently available describing the role of ^{18}F–FDG PET/CT for the noninvasive prediction of response to chemotherapy in advanced EOC. This study evaluated the hypothesis that changes in FDG uptake early in the course of treatment allow predicting the effectiveness of chemotherapy and subsequent patient outcome. The aim of this study was to prospectively evaluate the use of sequential metabolic ^{18}F–FDG PET/CT imaging at baseline, after the debulking surgery and after third cycle of chemotherapy and to compare changes in tumoral FDG uptake with progression-free survival (PFS) serving as the gold standard.

Materials and Methods

Patients

We prospectively enrolled consecutive patients with advanced epithelial ovarian cancer who underwent serial ^{18}F–FDG PET/CT at Seoul National University Hospital between October 2010 and October 2013. All clinical, histological, and imaging data from patients were collected and stored in a computerized database. Patients were required to have undergone preoperative integrated ^{18}F–FDG PET/CT imaging in the 2 weeks prior to surgery and 1 week prior to chemotherapy. Patients were excluded from analysis if they (1) were previously diagnosed with another malignant disease, (2) had a follow-up duration <6 months, or (3) received a primary treatment other than surgery, such as neoadjuvant chemotherapy. After treatment, all patients were clinically and radiologically followed up according to institutions' protocol. The study protocol was approved by the institutional review board, and informed consents were obtained from all patients.

Demographic and clinical characteristics and survival data were obtained from the patients' medical records and institutional tumor records. Tumor histology, grade, and size were obtained from the surgical pathology report.

^{18}F–FDG PET/CT

^{18}F–FDG PET/CT imaging was performed at baseline, 3 weeks after the debulking surgery and 3 weeks after third cycle of chemotherapy. The patients were studied using a dedicated PET/CT system (Gemini, Philips Medical Systems, Andover, MA, USA). Each patient was asked to fast for at least 4 h prior to undergoing PET/CT. A barium sulfate solution (125 mL EZCT: 1.5% weight–volume barium sulfate suspension; Taejoon Pharm, Seoul, Korea) was administered orally 1 h prior to imaging to opacify the bowel for the CT portion of the study. Diuretics were not used for preparation. In addition, 0.15 mCi/kg body weight of FDG was administered intravenously 1 h prior to imaging. CT was performed before PET; the resulting data were used to generate an attenuation correction map for PET, and the PET images were reconstructed. The following parameters were used for CT: 80 mAs, 120 kV, 5 mm section thickness, 0.5 s per rotation, and reconstruction onto a 512 × 512 matrix. Each PET scan was acquired from skull base to proximal thigh in three-dimensional row action

maximum likelihood algorithm mode with four iterations, eight subsets, and 4.8 mm full-width half-maximum reconstruction onto a 512 × 512 matrix. A total of 7 to 9 bed positions were examined for PET acquisition, with 2.5 min per bed.

Image Analysis

The PET/CT images were reviewed on an interactive video display provided by the equipment manufacturer. The maximum and average standardized uptake values (SUV_{max} and SUV_{avg}) were then quantitatively used to determine ^{18}F–FDG avidity. The SUV_{max} was calculated as follows: $SUV_{max} = C_{max} \times TBW/IA$, where C_{max} is the activity concentration in the voxel of highest tumor activity (Bq/mL); TBW is total body weight (kg); and IA is injected activity (kBq) [12,13].

Metabolic tumor volume (MTV) was measured from attenuation-corrected ^{18}F–FDG PET/CT images using an SUV-based automated contouring program (Syngo MI applications, Volumetric Analysis 6.0.14.4, Siemens Medical Solutions), and total lesion glycolysis (TLG) was calculated by multiplying the SUV_{avg} of the tumors by the metabolic volume of the tumor as previously described [14]. Two experienced nuclear medicine physicians from each institution interpreted the PET/CT images independently.

The volume of interest (VOI) was drawn to encompass the lesion and adjusted to remove physiological FDG uptake. Nuclear medicine physicians interactively selected each hypermetabolic lesion by clicking on its projection via a graphical user interface. The contour around the target lesions inside the boundaries was automatically produced, the voxels presenting a threshold of 40% SUV_{max} in the VOI within the contouring margin were incorporated to accurately define the tumor volumes. For each lesion in a given patient, functional criteria were determined from the serial ^{18}F–FDG PET/CT scans. As the anatomy before and after surgery may be completely different, ^{18}F–FDG PET/CT scans of 3 weeks after the debulking surgery was regarded as the reference of the scans of 3 weeks after third cycle of chemotherapy. In patients with suboptimal debulking surgery, residual lesions were also checked and followed. Although the post-surgical inflammation cannot be totally ignored after 3 weeks, we considered this factor in the measurement of VOI. Diffuse and mild abdominal or pelvic hypermetabolism without definitive hypermetabolic focus was regarded as post-surgical inflammation. Throughout the follow-up process, same VOIs were used for all measurements in each patient.

Tumor Glucose Metabolism Measurements

A spheroidal volume of interest encompassing the primary tumor or surrounding tissues was drawn to measure the SUV at baseline ($preopSUV_{max}$), 3 weeks after operation ($postopSUV_{max}$) and 3 weeks after third cycle of chemotherapy ($postchemoSUV_{max}$). The metabolic response was calculated as follows:

$$postop\Delta SUV_{max} = (preopSUV_{max} - postopSUV_{max})/preopSUV_{max}$$

$$postchemo\Delta SUV_{max} = (preopSUV_{max} - postchemoSUV_{max})/preopSUV_{max}$$

Clinical Evaluation

Tumor histologic cell type, grade, stage at cytoreductive surgery, site of metastasis, recurrence, and adjuvant treatment were recorded from the patient's medical record. A stage after cytoreductive surgery was assigned according to the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system [15]. Optimal cytoreduction was defined as resection without macroscopic residual

Table 1. Clinicopathological Characteristics of Patients Who Underwent Serial PET/CT for Epithelial Ovarian Cancer (n = 13)

| Characteristic	Patients	%
Age, median (range)	55 (42–75)	
Median PFS, months (range)	25 (13–34)	
FIGO stage		
IIIB	2	15.4
IIIC	11	84.6
Histology		
Serous adenocarcinoma	7	53.8
Endometrioid adenocarcinoma	3	23.1
Clear cell carcinoma	1	7.7
Transitional cell carcinoma	1	7.7
Mucinous adenocarcinoma	1	7.7
Preoperative CA 125	764 (61.7–3545)	
Optimal debulking	10	76.9
Recurrence	5	38.5

PFS, progression-free survival; *FIGO*, International Federation of Gynecology and Obstetrics.

Table 2. PET/CT Parameters of Patients Who Underwent Serial PET/CT for Epithelial Ovarian Cancer (n = 13)

Parameters	Median	Range
Preop SUV_{max}	13.07	2.44–30.30
Preop MTV_{tumour}	48.46	11.20–521.08
Preop TLG_{tumour}	545.35	42.79–3855.99
Postop SUV_{max}	2.26	1.52–9.03
Postop MTV_{tumour}	14.66	1.91–42.05
Postop TLG_{tumour}	53.59	8.58–103.87
Postchemo SUV_{max}	1.86	1.37–2.65
Postchemo MTV_{tumour}	5.27	2.19–13.59
Postchemo TLG_{tumour}	11.33	3.35–17.12
Postop ΔSUV_{max}	0.7016	-0.22–0.93
Postchemo ΔSUV_{max}	0.8577	-0.25–1.00

Preop, preoperative; *Postop*, postoperative; *Postchemo*, postchemotherapy; *SUV*, standardized uptake value; *MTV*, metabolic tumor volume; *TLG*, total lesion glycolysis.

tumor while suboptimal as resection with macroscopic residual lesion. Patients received primary debulking surgery followed by at least six courses of platinum-based chemotherapy (paclitaxel 175 mg/m^2, carboplatin AUC 5). Time to recurrence was defined as date of commencement of surgery to date of histological or imaging evidence of recurrence. A diagnosis of recurrent tumor or distant metastasis was based on either a positive biopsy or unequivocal clinical or radiographic evidence of progression.
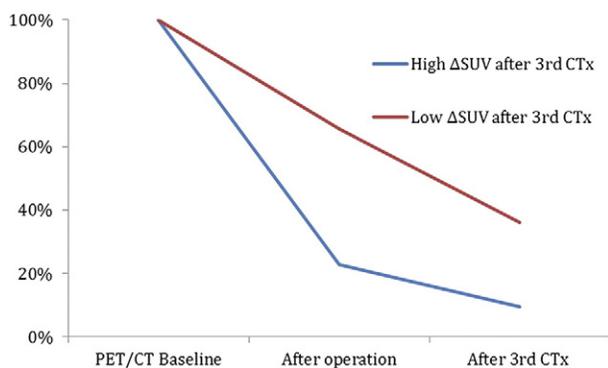
Figure 1. Relative changes in ^{18}F–FDG uptake expressed as SUV from baseline, 3 weeks after operation and after third cycle of chemotherapy treatment (CTx) in high and low ΔSUV groups after third cycle of chemotherapy.
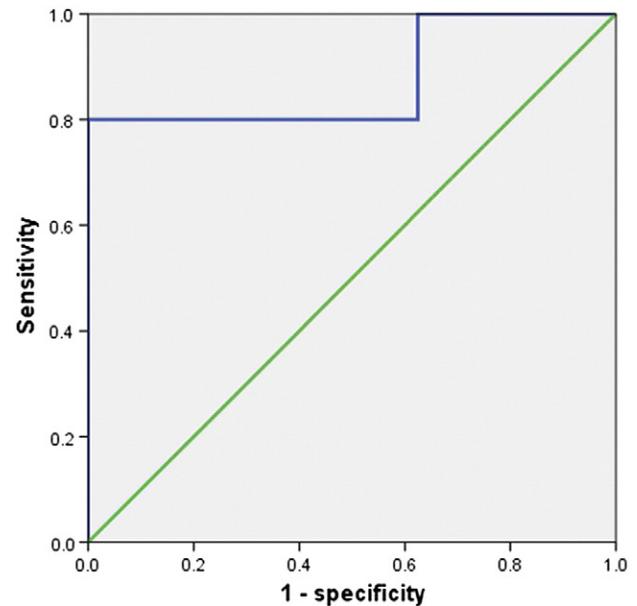
Figure 2. Receiver operating characteristic curve analysis for determining the cut-off value for ΔSUV after third cycle of chemotherapy for predicting recurrence. The area under the ROC curve of ΔSUV after third cycle of chemotherapy was 0.875, and −0.8277 was determined as the cut-off value (*P* = .028, sensitivity 80%, specificity 100%).

Statistical Analysis

We sought to determine the prognostic significance of metabolic parameters, and the changes of these parameters of tumor relative to PFS. Statistical analysis was performed using SPSS software for Windows (version 19.0; IBM SPSS, Somers, NY, USA). Time to event was calculated as the time interval from the date of surgery to the date of the first finding on clinical or imaging exam that suggested local, regional, or distant disease recurrence. The most discriminating threshold value allowing differentiation of the two groups of patients was selected using receiver-operating characteristic (ROC) methodology [16]. Survival rates were estimated according to Kaplan–Meier. Statistical comparisons between different groups of patients were performed with a log-rank test and the proportional hazard model. All tests are two sided and are performed at the 5% level of significance.

Table 3. Analyses of Prognostic Factors for Progression-Free Survival in Patients Who Underwent Serial PET/CT for Epithelial Ovarian Cancer (n = 13)

Variables	Test for progression-free survival	Hazard ratio	95% confidence interval	P
Age (years)		1.081	0.979–1.194	0.122
Tumor grade	3 versus 1, 2	0.971	0.162–5.818	0.974
Preop SUV_{max}		0.919	0.813–1.038	0.172
Preop MTV_{tumour}		0.991	0.973–1.010	0.352
Preop TLG_{tumour}		0.998	0.996–1.001	0.174
Postop ΔSUV_{max}		43.011	1.148–1611.600	0.042
Postop ΔMTV_{tumour}		2.153	0.362–12.807	0.399
Postop ΔTLG_{tumour}		8.019	0.398–168.406	0.177
Postchemo ΔSUV_{max}		7.405	0.352–155.870	0.198
Postchemo ΔMTV_{tumour}		0.253	0.000–3279.768	0.776
Postchemo ΔTLG_{tumour}		0.006	0.000–1.918E+ 15	0.803
Preoperative CA 125		0.999	0.998–1.001	0.305
Optimal debulking	No versus Yes	2.237	0.359–13.957	0.389
Postchemo ΔSUV_{max}	≤ 0.8277 versus >0.8277	17.284	1.851–161.406	0.012

FIGO, International Federation of Gynecology and Obstetrics; *Preop*, preoperative; *Postop*, postoperative; *Postchemo*, postchemotherapy; *SUV*, standardized uptake value; *MTV*, metabolic tumor volume; *TLG*, total lesion glycolysis.

Table 4. Multivariate Analyses of Prognostic Factors for Progression-Free Survival in Patients Who Underwent Serial PET/CT for Epithelial Ovarian Cancer (N = 13)

Variables	Test for progression-free survival	Hazard ratio	95% confidence interval	P
Age (years)		1.063	0.936–1.206	0.348
Postop ΔSUV_{max}		0.537	0.005–52.599	0.791
Postchemo ΔSUV_{max}	≤ 0.8277 versus >0.8277	16.375	1.041–257.536	0.047

Results

Patient Characteristics

A total of 13 patients meeting the eligibility criteria for this study were included in the analyses. The median follow-up for surviving patients was 25 months (range, 13 to 34 months). Clinicopathological findings of enrolled patients are summarized in Table 1. Table 2 depicts baseline and serial PET/CT parameters of patients. Figure 1 shows the relative changes in ^{18}F-FDG uptake in high and low ΔSUV groups according to treatment.

Measurement of Cut-Off Value of PostchemoΔSUV_{max}

Receiver operating characteristic curve analysis for determining the cut-off value for postchemoΔSUV_{max} after third cycle of chemotherapy for predicting recurrence was used. The area under the ROC curve of postchemoΔSUV_{max} was 0.875, and 0.828 was determined as the cut-off value with sensitivity of 80% and specificity of 100% (P = .028, Figure 2).

Correlation Between Parameters

In the current study, postchemoΔSUV_{max} correlated with postopΔSUV_{max} (P = .015), PFS (P = .033), and preopSUV$_{max}$ (P =.035). PostopΔSUV_{max} correlated with optimal debulking (P = .004), and PFS (P = .049).

Volumetric Tumor Markers

As shown in the Table 2, the median and highest values of SUV, MTV and TLG were all decreased with treatment. However, as summarized in the Table 3, the changes of volumetric functional markers such as MTV and TLG were not associated with patient outcome in this analysis.

Prediction of Recurrence

We compared survival outcomes according to clinicopathological variables and metabolic functional parameters using regression analyses (Table 3). In univariate regression analysis, low postopΔSUV_{max} (P = .042), and low postchemoΔSUV_{max} (P = .012) were significantly associated with recurrence.

In multivariate Cox proportional hazard analysis, low postchemoΔSUV_{max} was demonstrated as independent risk factors of recurrence in this study with a hazard ratio of 16.375 (Table 4). Kaplan–Meier survival graphs showed a significant difference in PFS between the groups categorized by postchemoΔSUV_{max} (Figure 3). Figure 4 depicts two representative cases of high and low postchemoΔSUV_{max}. Survival difference between groups categorized by postchemoΔSUV_{max} was statistically significant (P = .001, log-rank test). Table 5 summarizes the clinicopathological and PET/CT derived characteristics of patients with and without recurrence.

Discussion

The aim of this study was to prospectively evaluate the use of sequential metabolic ^{18}F–FDG PET/CT imaging at baseline, after the debulking surgery and after third cycle of chemotherapy. This study prospectively demonstrates that ^{18}F–FDG PET/CT identified patients with a poor prognosis after debulking surgery followed by third cycle of combination chemotherapy. The principle finding of this study was that low metabolic change during treatment on FDG PET/CT is the most powerful significant prognostic tool for predicting recurrence in advanced EOC. To the best of our knowledge, this is the first study to report the prognostic value of sequential metabolic imaging in advanced EOC in primary debulking setting.
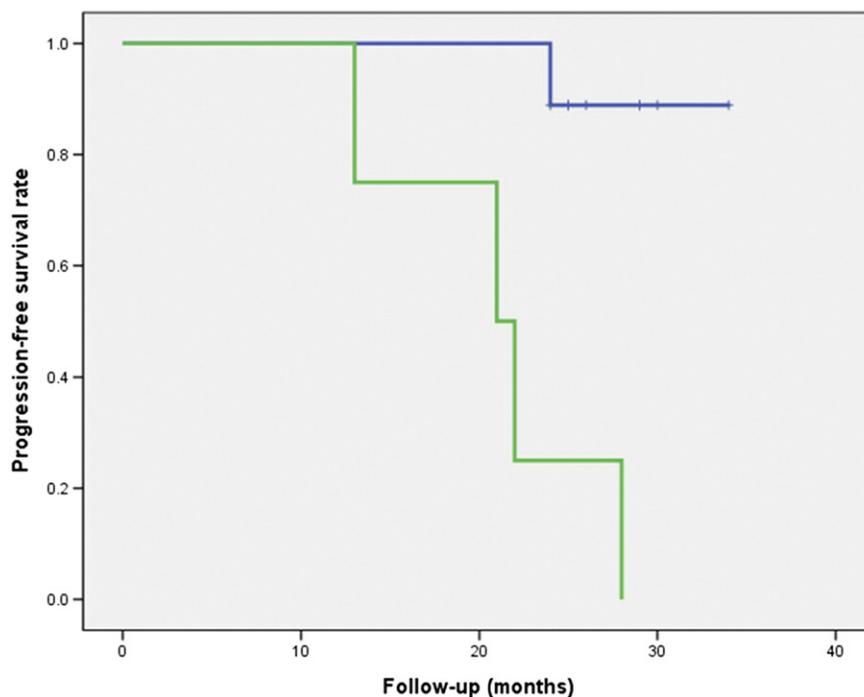
Figure 3. The Kaplan–Meier survival graph of ΔSUV after third cycle of chemotherapy and progression-free survival with ΔSUV above (blue line) and below (green line) cut-off value. Low ΔSUV after third cycle of chemotherapy was associated with shorter progression-free survival (P = .001, log-rank test).
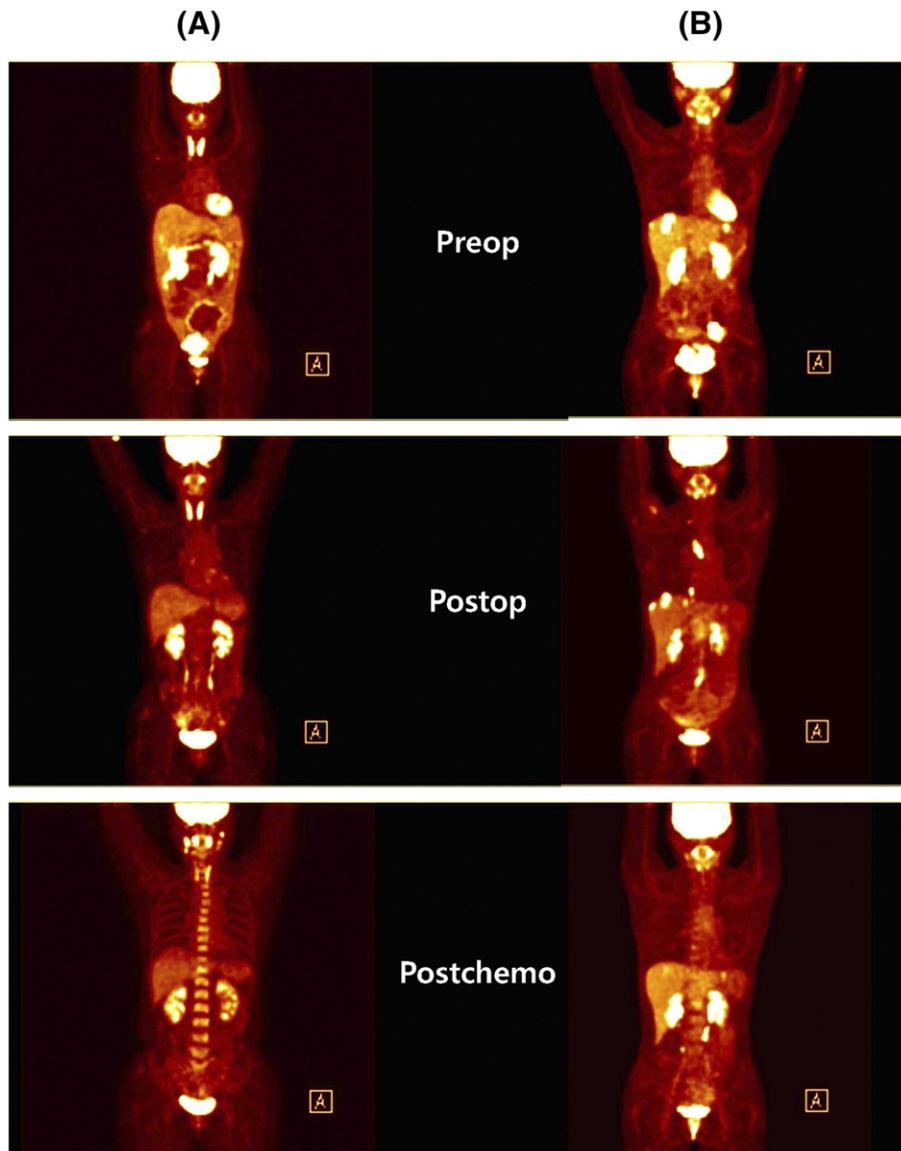
Figure 4. Two representative cases. (A) Fifty-five-year old female with FIGO stage IIIC serous ovarian cyst adenocarcinoma. Preoperative maximal standardized uptake value (SUV_{max}) was 9.7, postoperative SUV_{max} was 3.1, and postchemotherapy SUV_{max} was 0.9, and postchemoΔSUV_{max} was 0.907 which was a relatively high value among enrolled subjects. Recurrence did not occur during the follow-up period. (B) Forty-two-year old female with FIGO stage IIIC serous ovarian cyst adenocarcinoma. Preoperative SUV_{max} was 10.8, postoperative SUV_{max} was 6.1, and postchemotherapy SUV_{max} was 3.0, and postchemoΔSUV_{max} was 0.722 which was a relatively low value among enrolled subjects. Recurrence occurred 22 months after operation.

Table 5. Clinicopathological and PET/CT Derived Characteristics of Patients Without and With Recurrence (N = 13)

| Variable | Non-recurrent (N = 8) | | Recurrent (N = 5) | | |
	Mean	SD	Mean	SD	P
Age (year)	52.13	8.46	62.60	12.86	0.101
PFS (months)	27.75	3.37	21.60	5.50	0.028
SUV_{max}	17.92	8.65	10.56	7.21	0.142
Preop MTV_{tumour}	163.53	193.07	46.70	45.53	0.217
Preop TLG_{tumour}	1134.44	1192.57	340.60	378.63	0.182
Postop ΔSUV_{max}	0.75	0.13	0.46	0.45	0.105
Postchemo ΔSUV_{max}	0.90	0.06	0.70	0.26	0.048

SD, standard deviation; *PFS*, progression-free survival; *SUV*, standardized uptake value; *MTV*, metabolic tumor volume; *TLG*, total lesion glycolysis.

We focused our study on pretreatment ^{18}F–FDG PET/CT parameters, with the goal of identifying a measurement that could help to identify a high-risk group of patients that might experience recurrence. Current evidence suggests that metabolic change during treatment is an important predictor of recurrence than previously known clinicopathological parameters in advanced EOC.

Although age was not a significant risk factor of recurrence in univariate regression analysis, we included age in the multivariate analysis as it is a well-known conventional risk factor with borderline significance in univariate analysis. Low postchemoΔSUV_{max} was identified as independent risk factors of recurrence in this study, and this finding is unique in the current study despite small number of patients. However, much work needs to be done to establish the clinical role of sequential ^{18}F–FDG PET/CT in therapeutic assessment of EOC.

Over the past years, there is growing evidence that metabolic imaging by ^{18}F–FDG PET/CT provides useful information about response to treatment in a variety of solid tumors [6,17,18]. In EOC, previous study demonstrated close correlation between the early decrease in glucose metabolism and patient survival, showing over half the decrease in FDG uptake after the first cycle of neoadjuvant chemotherapy in responders [9]. Investigators also suggested clinical application of sequential FDG PET imaging in predicting response to during early stage of treatment. For clinical use, it is important to identify an optimal threshold for decrease in FDG uptake to classify metabolic responders from non-responders.

In the current study, one patient (71-year-old, serous adenocarcinoma, FIGO stage IIIB) with a high postchemoΔSUV$_{max}$ (0.923) in FDG uptake after the third cycle of chemotherapy had experienced recurrence 2 years after treatment. Other four patients with recurrence were classified as low postchemoΔSUV$_{max}$ in FDG uptake.

^{18}F–FDG PET/CT after the third cycle of chemotherapy provided strong prognostic information, and was significantly correlated with the PFS (P = .001). Optimal tumor-free cytoreduction is regarded as the critical factor of prognosis in patients with advanced EOC, and the prognosis depends on both successful surgery and chemotherapy [1]. In the current study, optimal cytoreduction was achieved in 10 patients with suboptimal debulking in 3 patients. Macroscopically optimal cytoreduction was achieved in 100% of high postchemoΔSUV$_{max}$ compared with 50% in patients with low postchemoΔSUV$_{max}$. Among the 10 patients with optimally debulked, 2 patients experienced recurrence, and 2 among 3 with sub-optimally debulked experienced recurrence. Because it is virtually impossible to surgically remove all tumor deposits in the peritoneal cavity, survival and prognosis is ultimately determined by the response to chemotherapy.

Recently, various molecular markers, genetic profiling, circulating tumor cell, and in vitro chemosensitivity test have been suggested to be helpful in predicting treatment response in EOC [19,20]. However, these approaches had principal limitations including the need for adequate tissue samples, tumor heterogeneity, as well as host factors such as drug delivery and metabolism that may not be reflected by gene expression profiles of the tumor cells [9]. The FDG uptake in tumors affected by the blood supply, fraction of hypoxic tissue, cellular proliferation and numerous enzyme systems determining the metabolic activity. However, ^{18}F–FDG PET/CT has been shown to provide a stable and highly reproducible signal in metabolically active tumors, reflecting an integral over various factors. An invaluable advantage of imaging changes in tumoral metabolic activity by ^{18}F–FDG PET/CT is the ability to monitor in vivo the overall result of therapeutic effects, not only in primary tumors but also in metastatic lesions throughout the body.

Limitations to our study include small group size and short follow-up. The number of patients was small, and the median follow-up duration short. Therefore, interpretation of the current study must be confined to short-term outcome, which implies a limited period of follow-up. Thus, response-guided planning of the treatment stratification might be tested in large clinical trials. Second, we could not analyze overall survival because there was no case of disease-related mortality among the study population, and the study period was relatively short. A technical factor should be considered while reviewing the cut-off values of the current study. Measurements performed in this study may not reflect the absolute values obtained elsewhere. Therefore, additional large prospective studies are necessary to confirm the predictive value of sequential ^{18}F–FDG PET/CT in clinical practice. Nevertheless, this report is noteworthy because it is the first study to show the prognostic value of sequential ^{18}F–FDG PET/CT in patients with untreated advanced EOC, and our findings suggest the need for further studies on metabolic parameters.

In conclusion, we demonstrated for the first time that high postchemoΔSUV$_{max}$ measured by serial ^{18}F–FDG PET/CT was an independent prognostic indicator of recurrence in patients with advanced EOC. Metabolic functional parameter can be useful quantitative criteria for disease prognostication in patients with advanced EOC during treatment. Early prediction of response might be helpful in treatment stratification of advanced EOC patients undergoing adjuvant chemotherapy that needs to be validated in large prospective studies.

Compliance with Ethical Standards

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