Eur J Nucl Med Mol Imaging (2014) 41:1898–1906
DOI 10.1007/s00259-014-2803-x

ORIGINAL ARTICLE

The role of metabolic tumor volume and total lesion glycolysis on ^{18}F-FDG PET/CT in the prognosis of epithelial ovarian cancer

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Received: 6 February 2014 / Accepted: 5 May 2014 / Published online: 23 May 2014

Abstract
Purpose This study assessed the prognostic value of pre-operative 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) volumetric parameters, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), in patients with epithelial ovarian cancer.
Methods A total of 175 patients with epithelial ovarian cancer who underwent ^{18}F-FDG PET/CT and subsequent cytoreductive surgery were retrospectively enrolled. Maximum standardized uptake value (SUVmax) on ^{18}F-FDG PET/CT was measured for all patients. Because nine patients showed low tumor-to-background uptake ratios, MTV and TLG were measured in 166 patients. Univariate and multivariate analyses were performed to evaluate the prognostic significance of SUVmax, MTV, TLG, and clinicopathological factors for disease progression-free survival.
Results Disease progressed in 78 (44.6 %) of the 175 patients, and the 2-year disease progression-free survival rate was 57.5 %. Univariate analysis showed that tumor stage, histopathological type, presence of regional lymph node metastasis, residual tumor after cytoreductive surgery, pre-operative serum carbohydrate antigen 125 (CA125) level, SUVmax, MTV, and TLG were significant prognostic factors ($p < 0.05$). Among these variables, tumor stage ($p=0.0006$) and TLG ($p=0.008$) independently correlated with disease progression-free survival on multivariate analysis. The disease progression rate was only 2.3 % in stage I-II patients with low TLG (≤100.0), compared to 80.0 % in stage III-IV patients with high TLG (>100.0).
Conclusion Along with tumor stage, TLG is an independent prognostic factor for disease progression after cytoreductive surgery in patients with epithelial ovarian cancer. By combining tumor stage and TLG, one can further stratify the risk of disease progression for patients undergoing cytoreductive surgery.

Keywords Ovarian cancer · ^{18}F-fluorodeoxyglucose PET · Metabolic tumor volume · Total lesion glycolysis · Prognosis

Introduction

Ovarian cancer is the eighth most common malignancy among women and has the highest mortality rate of any gynecologic malignancy [1]. Epithelial ovarian cancers are the most common ovarian cancers and the majority of patients with epithelial ovarian cancers are diagnosed at an advanced stage [2]. Although cytoreductive surgery along with platinum and paclitaxel combination chemotherapy has improved outcomes, the prognosis of patients with epithelial ovarian cancer is still poor, with a 5-year overall survival rate less than 50 % [2, 3]. Identifying the prognostic factors for epithelial ovarian cancer is important to predict outcomes and allow the planning of the most appropriate treatment. Several factors including age, International Federation of Obstetrics and Gynecology (FIGO) stage, histopathological type, tumor grade, residual tumor after primary cytoreductive surgery, adjuvant chemotherapy, regional lymph node metastases, and serum carbohydrate antigen 125 (CA125) level have been shown to have significant predictive value [4–9].

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Currently, 2-[^{18}F] fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been widely used in various malignant tumor types. In patients with epithelial ovarian cancer, ^{18}F-FDG PET/CT is useful in diagnosing, staging, detecting recurrent lesions, and monitoring treatment response [10–14]. Furthermore, the degree of ^{18}F-FDG uptake of ovarian cancer lesions, expressed as the maximum standardized uptake value (SUVmax), was found to be a significant parameter for predicting clinical outcome [15–18]. In addition to SUVmax, recent studies have demonstrated that other ^{18}F-FDG PET/CT-based volumetric parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are also significant prognostic factors in various cancers [19–22]. However, there are few studies that have evaluated MTV and TLG as prognostic factors in epithelial ovarian cancer [23, 24]. In this study, we assessed the prognostic value of volumetric parameters on pre-operative ^{18}F-FDG PET/CT and compare their predictive values with those of other conventional prognostic factors in patients with epithelial ovarian cancer.

Materials and methods

Patients

This retrospective study was approved by the institutional review board of our medical center, and the need for written informed consent was waived. The electronic medical records of patients with newly diagnosed epithelial ovarian cancer who underwent pre-operative ^{18}F-FDG PET/CT and subsequent surgical staging between January 2008 and June 2012 were retrospectively reviewed, and a total of 191 patients were enrolled in the study. Patients were excluded from the study if they (1) had previous history of another malignancy, (2) received any kind of neoadjuvant treatment prior to surgery, (3) were lost to follow-up, or (4) were diagnosed with multiple primary gynecologic cancers on surgical staging. The mean interval between pre-operative ^{18}F-FDG PET/CT imaging and cytoreductive surgery was 5.8±4.5 days (median, 5.0 days). All enrolled patients also underwent conventional radiologic imaging with contrast-enhanced CT and/or magnetic resonance imaging (MRI). Furthermore, serum CA125 levels were measured prior to surgery.

All enrolled patients underwent an FIGO staging operation consisting of bilateral salpingo-oophorectomy, hysterectomy, lymphadenectomy, omentectomy, and maximal tumor reduction [2]. Moreover, biopsies were performed for all suspicious sites such as the mesentery, liver, diaphragm, pelvis, and para-aortic lymph nodes. A stage was assigned based on the operative findings and histopathological results according to the FIGO staging system for ovarian cancer [2]. Patients received platinum-based adjuvant chemotherapy after operation if indicated by their FIGO stage, and if their clinical condition permitted. All patients underwent clinical follow-up that included diagnostic imaging studies and blood tests after cytoreductive surgery. The mean duration of clinical follow-up was 31.8±16.3 months (median, 30.7 months). During follow-up, clinical assessment was performed every 2–3 months, and blood tests, including serum CA125 level and imaging studies such as contrast-enhanced CT scan were performed every 6–8 months. In addition, follow-up ^{18}F-FDG PET/CT were performed in patients with advanced stage or high risk of recurrence. If the clinical assessment or studies performed during follow-up showed an abnormal finding, additional diagnostic studies and/or histopathological confirmation were performed to assess cancer recurrence or disease progression.

^{18}F-FDG PET/CT

All ^{18}F-FDG PET/CT scans were performed using a dedicated PET/CT scanner (Discovery STe, GE Healthcare; or Biograph TruePoint 40, Siemens Healthcare). All patients fasted for at least 6 h prior to the PET/CT imaging. PET/CT images were acquired 60 min after intravenous injection of approximately 5.5 MBq/kg ^{18}F-FDG. First, a CT scan was performed at 30 mA and 130 kVp with the Discovery STe scanner, or at 36 mA and 120 kVp with the Biograph TruePoint scanner, without contrast-enhancement. Afterwards, a PET scan was performed extending from the skull base to the proximal thighs with an acquisition time of 3 min per bed position in 3D mode. PET images were reconstructed using ordered subset expectation maximization (OSEM) with attenuation correction.

The analysis of ^{18}F-FDG PET/CT images was performed using an Advantage Workstation 4.4 (GE Medical Systems). First, SUVmax for each patient was calculated by placing a spheroid-shaped volume of interest (VOI) at the primary tumor lesion and metastatic lesions. The SUV was calculated as (decay-corrected activity [kBq] per milliliter of tissue volume)/(injected ^{18}F-FDG activity [kBq] per gram of body mass). Afterwards, MTV and mean SUV of the primary tumor and metastatic lesions were measured as follows [20]; first, an elliptical VOI was drawn fully encasing the primary ovarian lesion and all metastatic lesions in the transaxial, sagittal, and coronal PET/CT images. Secondly, the boundaries of voxels, the SUV of which exceeded a threshold of 40 % of SUVmax, were automatically produced. The 40 % SUVmax threshold was shown to best fit the actual volume of simulating phantom lesions in previous studies [25, 26]. Thirdly, the voxels of normal organs such as heart, liver, kidneys, ureters, and bladder, as well as false-positive lesions such as inflammatory lesions or other benign lesions were manually subtracted. Finally, MTV and mean SUV of all primary tumors and

metastatic lesions were measured. TLG was calculated as (MTV) × (mean SUV).

Statistical analysis

After surgery, the patients were classified into two groups; (i) the recurrence group included patients who had either newly developed tumors or progression of residual tumors on follow-up, and (ii) the no recurrence group included patients with no evidence of cancer recurrence or progression of residual disease on follow-up. Clinicopathological factors, SUVmax, MTV, and TLG were compared between the two groups using the Student's t test and the chi-squared test. The mean values of SUVmax in tumors of different histopathological types were compared using the Kruskal-Wallis test. Kaplan-Meier survival analysis with a log-rank test was performed to calculate cumulative disease progression-free survival rates according to clinicopathological factors, SUVmax, MTV, and TLG. Events in the analysis of disease progression-free survival included the occurrence of new cancer lesions or progression of residual lesions. Progression-free survival time was defined as the time from surgical staging to the date of event detection or to the date of the last clinical follow-up. For statistical analyses, continuous variables, including age, serum CA125 level, SUVmax, MTV, and TLG, were grouped into two categories according to specific cutoff values. The optimal cutoff values were determined by using receiver-operating characteristic (ROC) curve analysis. The significance of the predictive values of tumor factors, SUVmax, MTV, and TLG was evaluated using the log-rank test on univariate analysis. Variables that were statistically significant on univariateanalysis were selected for multivariate analysis using the Cox proportional hazards regression test. To evaluate multi-colinearity between MTV and TLG, Spearman's rank correlation coefficient was calculated before multivariate analysis. Moreover, the Mann–Whitney test and chi-squared test were performed to compare ^{18}F-FDG PET/CT parameters between patients with residual cancer and without residual cancer after surgery. Statistical analyses were performed using SPSS 20.0 for Windows (SPSS Inc.), and p-values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

SUVmax, MTV and TLG could not be calculated in 16 of the 191 patients because of computational or technical problems. ^{18}F-FDG PET/CT images from the remaining patients were amenable for analysis, and finally 175 patients were enrolled in the study. MTV and TLG could not be measured in nine patients among 175 patients (mucinous carcinoma, four; serous carcinoma, three; clear cell carcinoma, one; endometrioid carcinoma, one) because of low tumor-to-background uptake ratios. Statistical analysis for MTV and TLG was performed in the remaining 166 patients. Among these nine patients, none showed a recurrence event during clinical follow-up.

The characteristics of the 175 enrolled patients are shown in Table 1. During clinical follow-up, cancer recurrence or progression of residual lesions were found in 78 patients (44.6 %). The 2-year disease progression-free survival rate was 57.5 %, and the median progression-free survival time was 30.3 months. Of the 175 patients, 166 (94.9 %) received adjuvant treatment after cytoreductive surgery. The mean values of SUVmax of serous, endometrioid, clear cell, mucinous, and mixed-type carcinomas were 10.3±3.7, 12.1±6.6, 8.8±8.2, 6.1±3.5, and 14.2±7.7, respectively ($p<0.0001$ for Kruskal-Wallis test). Serous and endometrioid carcinomas showed significantly higher SUVmax than mucinous carcinoma ($p=0.0004$ for serous carcinoma and $p=0.002$ for endometrioid carcinoma). The SUVmax, M,TV and TLG in patients with stage III and IV (11.0±3.7, 54.0±63.0 cm^3, and 422.4±514.5 g, respectively) were significantly higher than those in patients with stage I and II (8.4±6.2, 19.1±23.3 cm^3, and 115.3±139.6 g, respectively; $p=0.002$ for SUVmax and $p<0.0001$ for both MTV and TLG). Of the 175 patients, preoperative ^{18}F-FDG PET/CT detected extra-abdominal metastasis in eight patients (4.6 %) and retroperitoneal and/or abdominal lymph node metastasis in nine patients (5.1 %), which were not found on other diagnostic imaging modalities.

Comparison between the recurrence and no recurrence groups showed significant differences in age, histopathological type, FIGO stage, tumor grade, the presence of regional lymph node metastasis, residual tumor after cytoreductive surgery, pre-operative serum CA125 level, MTV, and TLG ($p<0.05$; Table 1). The MTV and TLG in the recurrence group (Fig. 1) were significantly higher than those in the no recurrence group ($p<0.05$); however, borderline significance was shown in SUVmax between the two groups ($p=0.06$). The distributions of SUVmax, MTV, and TLG in the recurrence and no recurrence groups are shown in Fig. 2.

Prognostic factors

Age, histopathological type, FIGO stage, tumor grade, regional lymph node metastasis, residual tumor after cytoreductive surgery, pre-operative serum CA125 level, SUVmax, MTV, and TLG were evaluated as variables in survival analysis. ROC curve analyses were performed for continuous variables, including age, serum CA125 level, SUVmax, MTV, and TLG, to specify cutoff values. The

Table 1 Patient characteristics according to recurrence

Variables		Total (n=175)	Recurrence (n=78)	No recurrence (n=97)	p-value
Follow-up duration (months)		31.8±16.3	32.9±15.3	31.0±17.1	0.4
Age (yr)		56.2±11.3	58.4±10.5	54.5±11.7	0.02
Histopathology					<0.0001
	Serous	113 (64.6 %)	65 (83.5 %)	48 (49.5 %)	
	Endometrioid	19 (10.9 %)	5 (6.4 %)	14 (14.4 %)	
	Clear cell	20 (11.4 %)	4 (5.1 %)	16 (16.5 %)	
	Mucinous	20 (11.4 %)	2 (2.5 %)	18 (18.6 %)	
	Mixed	3 (1.7 %)	2 (2.5 %)	1 (1.0 %)	
FIGO stage					<0.0001
	I	57 (32.6 %)	2 (2.5 %)	55 (56.7 %)	
	II	17 (9.7 %)	4 (5.1 %)	13 (13.4 %)	
	III	87 (49.7 %)	59 (75.7 %)	28 (28.9 %)	
	IV	14 (8.0 %)	13 (16.7 %)	1 (1.0 %)	
Tumor grade					0.001
	1	22 (12.6 %)	4 (5.1 %)	18 (18.6 %)	
	2	62 (35.4 %)	26 (33.3 %)	36 (37.1 %)	
	3	71 (40.6 %)	43 (55.2 %)	28 (28.9 %)	
	Unidentified	20 (11.4 %)	5 (6.4 %)	15 (15.4 %)	
Regional lymph node metastasis					<0.0001
	Positive	70 (40.0 %)	53 (67.9 %)	17 (17.5 %)	
	Negative	105 (60.0 %)	25 (32.1 %)	80 (82.5 %)	
Residual tumor after surgery					<0.0001
	Positive	45 (25.7 %)	33 (42.3 %)	12 (12.4 %)	
	Negative	130 (74.3 %)	45 (57.7 %)	85 (87.6 %)	
Serum CA125 (U/mL)		1276.4±2000.3	1929.6±2233.5	751.1±1620.5	0.0001
SUVmax		9.9±5.1	10.7±3.6	9.3±5.9	0.06
MTV (cm^3)*		40.3±54.0	61.0±63.5	22.0±35.2	<0.0001
TLG (g)*		302.1±436.6	478.8±558.1	145.5±181.7	<0.0001

*Calculated in 166 patients (recurrence, 78 patients; no recurrence, 88 patients)

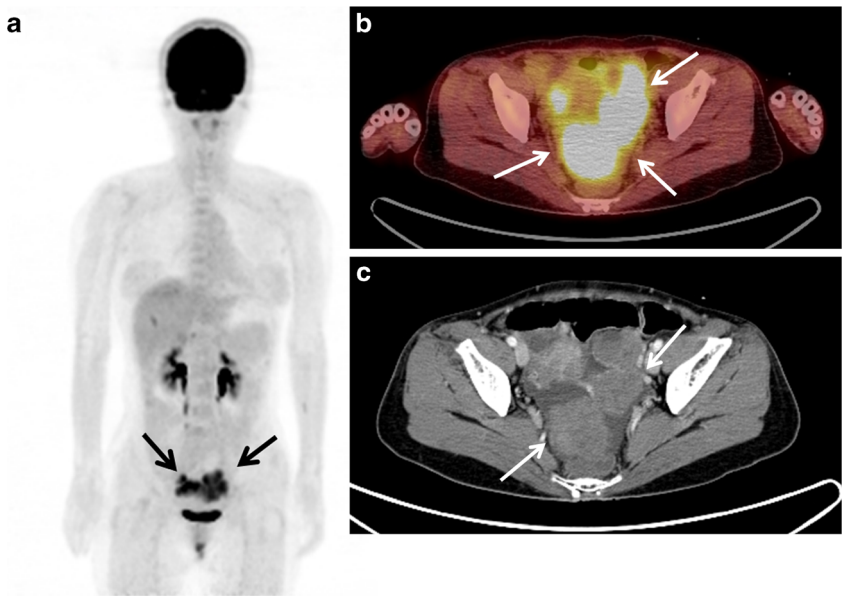

Fig. 1 The maximum intensity projection (**a**) and transaxial fused (**b**) ^{18}F-FDG PET/CT images and contrast-enhanced CT image (**c**) of a 56-year-old woman with serous carcinoma. Intensely increased ^{18}F-FD uptake is shown in the right ovarian mass lesion and metastatic lesions of the pelvic cavity with maximum SUV of 6.0. MTV and TLG of primary cancer and metastatic lesions were 38.3 cm^3 and 172.1 g, respectively. The patient underwent cytoreductive surgery and was surgically staged at stage III. The cancer was recurred 14 months after the surgery

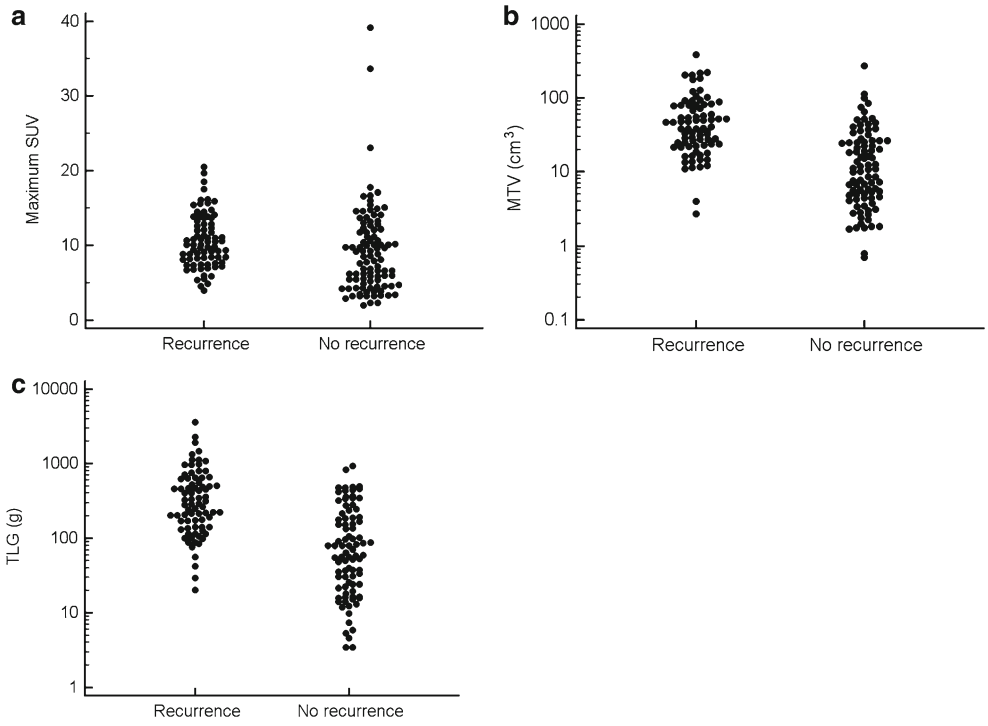

Fig. 2 Distributions of SUVmax (**a**), MTV (**b**), and TLG (**c**) on ^{18}F-FDG PET/CT for the recurrence (n=78) and no recurrence (n=97) groups

optimal cutoff values for age, serum CA125 level, SUVmax, MTV, and TLG were 55 years, 340 U/mL, 8.0, 25.0 cm^3, and 100.0 g, respectively. The significance of prognostic factors on univariateanalysis and 2-year progression-free survival rates according to the variables is shown in Table 2. Among the variables, histopathological type, FIGO stage, presence of regional lymph node metastasis, residual tumor after cytoreductive surgery, serum CA125 level, SUVmax, MTV, and TLG were significant on univariate analysis ($p<0.05$) and were selected for multivariate analysis. The cumulative disease progression-free survival curve according to the FIGO stage, SUVmax, MTV, and TLG by the Kaplan-Meier method is shown in Fig. 3. Because TLG is calculated by multiplying the MTV and mean SUV, multi-colinearity between MTV and TLG was evaluated before multivariate analysis. The result of the Spearman's rank correlation test showed a significant correlation between MTV and TLG ($r=0.920$, $p<0.0001$), thus MTV and TLG were separately assessed with other variables on multivariate analysis. Because MTV and TLG were calculated in 166 patients, multivariate analysis was performed in those 166 patients (Table 3). On multivariate analysis, only FIGO stage and TLG were statistically significant ($p<0.05$).

By combining FIGO stage with TLG, which were statistically significant variables on multivariate analysis, their predictive value could be further enhanced (Table 4). In patients with stage III-IV disease and TLG>100.0, the disease progression rate was high at 80.0 %, while patients with stage I-II disease and TLG≤100.0 g had a low disease progression rate of 2.3 %. The disease progression-free survival rates for patients with TLG≤100.0 g were significantly higher than those for patients with TLG>100.0 g in any stage of disease ($p=0.01$ for stage I-II and $p=0.009$ for stage III-IV; Fig. 4).

Table 2 Significance of prognostic factors on univariate analysis and 2-year disease progression-free survival rates (n=175)

Variables	2-year progression-free survival rate (%)		p-value
Age	≤ 55	67.2	0.07
	> 55	50.9	
Histopathology	Serous	49.3	0.0004
	Others	75.2	
FIGO stage	I-II	93.8	< 0.0001
	III-IV	34.7	
Tumor grade	1–2	64.0	0.06
	3	49.1	
Lymph node metastasis	Negative	76.6	< 0.0001
	Positive	30.8	
Residual tumor	Negative	67.1	< 0.0001
	Positive	31.8	
Serum CA125	≤ 340 U/mL	80.5	< 0.0001
	> 340 U/mL	39.2	
SUVmax	≤ 8.0	73.1	0.003
	> 8.0	48.9	
MTV*	≤ 25.0 cm^3	71.6	< 0.0001
	> 25.0 cm^3	39.5	
TLG*	≤ 100.0 g	83.8	< 0.0001
	> 100.0 g	40.1	

*Calculated in 166 patients

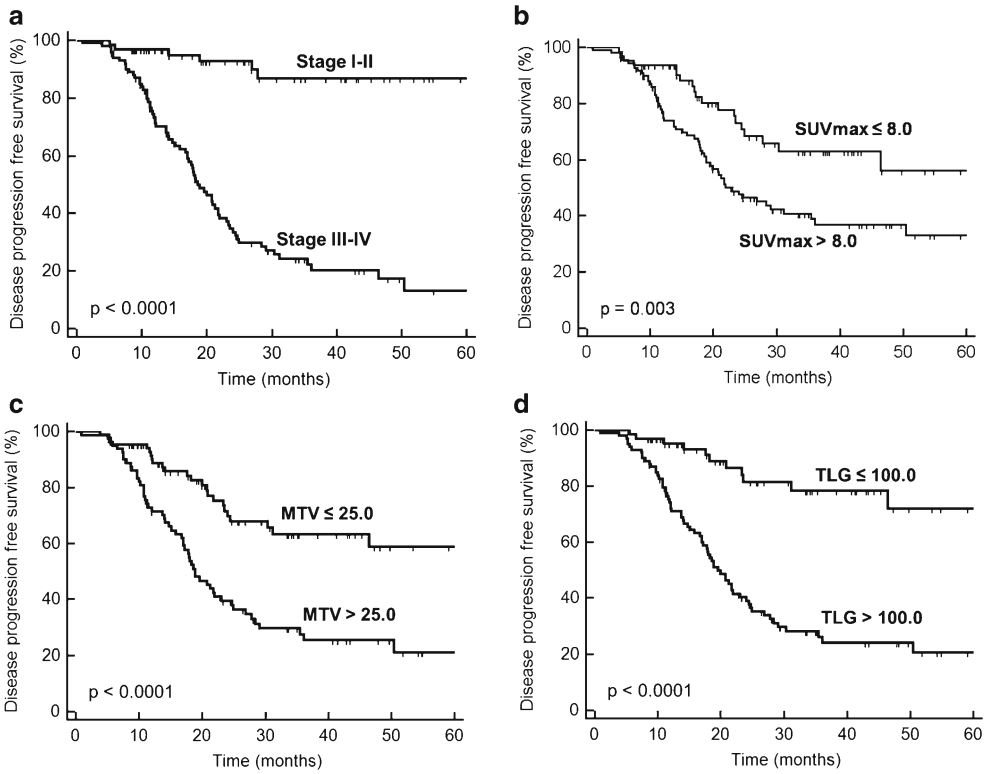

Fig. 3 The cumulative disease progression-free survival curves according to FIGO stage (**a**), SUVmax (**b**), MTV (**c**), and TLG (**d**)

Prediction of residual tumor

The patients with residual tumor after cytoreductive surgery had significantly higher values of SUVmax (11.6±3.5 vs. 9.3 ±5.4), MTV (59.0±55.0 vs. 33.4±52.1), and TLG (459.8± 434.8 vs. 243.5±424.3) than the patients with negative residual tumor ($p=0.0002$ for SUVmax and $p<0.0001$ for MTV and TLG). The incidence of residual tumor after operation according to the SUVmax, MTG, and TLG are shown in Table 5. There were significant differences of incidence rates of residual tumor according to the cutoff values of SUVmax, MTV, and TLG ($p<0.05$). Of 45 patients with residual tumor, 88.9 % (40 patients) had TLG>100.0 g. In patients with MTV>25.0 cm^3or TLG>100.0 g, 39.2 % had residual tumor after surgery.

Discussion

To the best of our knowledge, this is the largest clinical study to assess the prognostic significance of volumetric parameters derived from ^{18}F-FDG PET/CT in patients with epithelial ovarian cancer after cytoreductive surgery. Our study demonstrated that TLG of whole-body tumor burden on preoperative ^{18}F-FDG PET/CT is a significant independent prognostic factor, along with FIGO stage, for disease progression of epithelial ovarian cancer after cytoreductive surgery. Incorporation of TLG with FIGO stage can be more accurately prognostic than either TLG or FIGO stage alone.

SUVmax has been widely used as an indicator of metabolic activity for various malignancies. However, SUVmax only represents the highest metabolic activity within the tumor

Table 3 Significance of prognostic factors on multivariate analysis (n=166)

Variables	Multivariate (Model 1)		Multivariate (Model 2)	
	Hazard ratio (95 % CI)	p value	Hazard ratio (95 % CI)	p value
Histopathology	1.2 (0.6–2.5)	0.6	1.2 (0.6–2.5)	0.6
FIGO stage	6.3 (2.4–16.3)	0.0002	5.5 (2.1–14.4)	0.0006
Lymph node metastasis	1.6 (0.9–2.8)	0.1	1.5 (0.8–2.8)	0.2
Residual tumor	1.2 (0.7–1.9)	0.5	1.1 (0.7–1.8)	0.7
Serum CA125	1.8 (0.9–3.4)	0.07	1.6 (0.9–3.1)	0.1
SUVmax	0.8 (0.5–1.4)	0.4	0.8 (0.5–1.4)	0.4
MTV	1.5 (0.9–2.7)	0.1		
TLG			2.5 (1.3–4.8)	0.008

Table 4 Disease progression rates according to the combination of FIGO stage and TLG (n=166)

		FIGO stage	
		Stage I-II	Stage III-IV
TLG (g)	≤ 100	1/43 (2.3 %)	8/21 (38.1 %)
	> 100	5/22 (22.7 %)	64/80 (80.0 %)

and does not take the tumor extent into account [23, 25]. In contrast, MTV takes into account the metabolic active volume of all tumor lesions, which, in our study, is the sum of voxels over 40 % of SUVmax [25]. Furthermore, TLG considers both the level of tumor glucose utilization and the volume of metabolically active tumor lesions [27]. Hence, a large TLG can reflect a small volume of tumor lesion with high ^{18}F-FDG uptake or a large volume with low ^{18}F-FDG uptake [21]. Because TLG reflects both the metabolic burden and disease extent, it can provide a higher predictive value than SUVmax. The results of our study also showed that TLG was the only independent prognostic factor among SUVmax, MTV and TLG, and had a higher predictive value than SUVmax. However, in nine of the enrolled patients, MTV and TLG could not be measured because of the low tumor-to-background uptake ratios. Although none of these nine patients experienced disease progression or recurrence, it could be considered as a limitation for the clinical use of the volumetric parameters as compared to SUVmax. Further investigation for developing a method of measuring MTV in tumors with low ^{18}F-FDG uptake is needed.

To date, only one other study has investigated the predictive value of volumetric parameters on pre-operative ^{18}F-FDG PET/CT in patients with epithelial ovarian cancer [23]. Chung et al. [23] performed pre-operative ^{18}F-FDG PET/CT in 55 patients with epithelial ovarian cancer before surgical staging. The results of their study demonstrated that higher values of both MTV and TLG were associated with poor clinical outcome, and that MTV and TLG were statistically significant predictors of recurrence, which is similar to the results of our study. However, they showed that MTV was more predictive of recurrence than TLG, in contrast to our study. The difference in results between the two studies may be due to the different methodology of measuring MTV and TLG, and the different clinical characteristics of enrolled patients, especially the higher percentage of patients with advanced-stage disease in their study.

^{18}F-FDG PET/CT is known to be useful for detecting lymph node metastasis and extra-abdominal distant metastasis of epithelial ovarian cancer [13, 16, 28, 29], and, in our study, additional metastatic lesions were found by ^{18}F-FDG PET/CT in 9.7 % of enrolled patients. A recent study showed that ^{18}F-FDG PET/CT was even better than MRI for detecting recurrent small peritoneal implants [30]. Nonetheless, because epithelial ovarian cancer is surgically staged, and also because patients with extra-abdominal lesions on ^{18}F-FDG PET/CT also underwent cytoreductive surgery for a possible survival benefit, similar to patients negative for distant metastatic lesions, the role of pre-operative ^{18}F-FDG PET/CT was not clear [16]. The results of our study suggest that pre-operative ^{18}F-FDG PET/CT in epithelial ovarian cancer can provide information on prognosis after cytoreductive surgery, in addition to its original purpose of detecting metastatic lesions. Nevertheless, FIGO stage had greater predictive value for disease progression and none of the volumetric parameters on ^{18}F-FDG PET/CT could replace FIGO staging as a prognostic factor. However, it should be pointed out that the combination of FIGO stage with TLG can improve the prognostic stratification of patients with epithelial ovarian cancer. Among patients with stage I-II disease, the disease progression rate was high at 22.7 % if TLG on PET/CT was greater than 100.0 g.

The risk of residual cancer after cytoreductive surgery can be predicted by the volumetric parameters on ^{18}F-FDG PET/CT. The presence of residual cancer after a debulking operation has already shown to be a more powerful prognostic determinant than stage in a recent meta-analysis study [31]. According to the results of our study, 39.2 % of patients with high TLG had residual cancer, while less than 10 % of patients with low TLG had residual cancer after surgery. Hence,

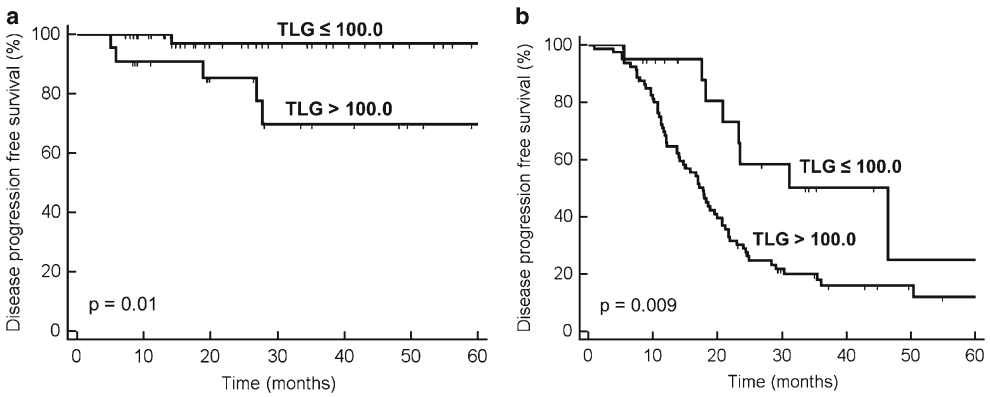

Fig. 4 The cumulative disease progression-free survival curves according to TLG in patients with stage I-II (**a**) and in patients with stage III-IV (**b**) disease

Table 5 The incidence of residual tumor after cytoreductive surgery according to the ^{18}F-FDG PET/CT parameters (n=175 for SUVmax and n=166 for MTV and TLG)

		Positive residual tumor	Negative residual tumor	P-value
SUVmax	≤ 8.0	7 (10.8 %)	58 (89.2 %)	0.001
	> 8.0	38 (34.5 %)	72 (65.5 %)	
MTV	≤ 25.0 cm^3	14 (16.1 %)	73 (83.9 %)	0.002
	> 25.0 cm^3	31 (39.2 %)	48 (60.8 %)	
TLG	≤ 100.0 g	5 (7.8 %)	59 (92.2 %)	<0.0001
	> 100.0 g	40 (39.2 %)	62 (60.8 %)	

patients with high TLG can be considered as having high risk of residual cancer and disease progression. In addition to detecting additional metastatic lesions, ^{18}F-FDG PET/CT could give information on the risk of residual cancer after surgery, which has a potential impact on planning treatment modality and performing adjuvant treatment.

In the present study, we measured whole-body metabolic tumor burden in the primary tumor lesion and all metastatic lesions using a threshold of 40 % SUVmax. Most previous studies evaluated MTV based on the tumor volume of the primary lesion only. Recent studies have used MTV as a measure of whole-body metabolic tumor burden and evaluated its prognostic value [20, 23, 32, 33]. Still, there is no consensus on whether whole-body metabolic tumor burden has greater predictive value than primary tumor volume. However, it stands to reason that MTV measuring whole-body metabolic tumor burden would be appropriate for epithelial ovarian cancer because most of these cancers have extensive metastatic lesions in the peritoneum or pelvic cavity at the time of diagnosis and it is often difficult to differentiate the volume of the primary tumor from that of adjacent peritoneal metastatic lesions.

Previous studies evaluating MTV mostly used three methods for defining threshold SUV to delineate metabolic tumor: (1) using a fixed SUV threshold such as 2.5 [19, 34] or 3.0 [20], (2) using a fixed ratio such as 40 % [23, 25, 26] or 50 % [33] of SUVmax as a threshold, or (3) using a threshold SUV of the mediastinal background SUV plus two standard deviations [34, 35]. There is still no established method of defining threshold SUV for clinical use. In the present study, we used a threshold of 40 % of SUVmax to define MTV. Previous studies using a phantom have demonstrated that an SUV of 40-50 % of the maximum was appropriate for contouring the actual tumor volume [25, 26]. In addition, physiologic ^{18}F-FDG uptake of SUV more than 2.5 or 3.0 in normal tissues of the abdomen does not allow the use of a fixed threshold of 2.5 or 3.0. Therefore, further studies comparing various methods for defining the threshold SUV are needed for standardization.

There are several limitations to the present study. First, because it was a single-center study with a retrospective design, selection bias was inherent and the general applicability of our study may therefore be limited. Second, a partial-volume effect may have affected the ^{18}F-FDG in small lesions, especially in small peritoneal lesions, resulting in underestimation of MTV and TLG values. Lastly, because of the small number of enrolled patients, subgroup analysis according to histopathology could not be performed. Although serous, endometrioid, clear cell, and mucinous ovarian carcinomas are lumped together as epithelial ovarian cancers, in reality, they are clinically, morphologically, and molecularly distinct cancers that bear little resemblance to each other [36].

In conclusion, TLG, a volumetric parameter on ^{18}F-FDG PET/CT representing metabolically active tumor burden, was a significant independent prognostic factor for disease progression after cytoreductive surgery in patients with epithelial ovarian cancer, in addition to FIGO stage.^{18}F-FDG PET/CT found additional metastatic lesions in 9.7 % of total patients and also showed additional value for predicting prognosis after surgery. None of the volumetric parameters on ^{18}F-FDG PET/CT could replace FIGO staging as a prognostic factor; however, by combining TLG with stage, prognostic stratification of the patients was further improved. Further multi-center prospective studies with larger cohorts of patients are needed to validate the results of our study.

Acknowledgments This study was supported by a National Research Foundation of Korea Grant funded by the Korean Government (NRF-2011–013-E00038, No. 2012027176) and the National R&D Program for Cancer Control, Ministry of Health & Welfare (1320210).

Conflict of interest The authors declare that they have no conflicts of interest.

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