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Prognostic Value of Pre- and Post-Treatment FDG PET/CT Parameters in Small Cell Lung Cancer Patients

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Abstract
Purpose To evaluate the prognostic value of PET parameters obtained from pre- and post-treatment FDG PET/CT examinations in patients with SCLC.
Methods Fifty-nine patients with initially diagnosed SCLC from 2009 to 2014 were included and had chemotherapy and/or concurrent chemoradiotherapy. FDG PET/CT examinations were performed before (PET1) and after (PET2) treatment to evaluate treatment response. A region of interest was placed over the primary lesion and metastatic lymph nodes within the thoracic cavity. PET parameters including change from PET1 to PET2 (Δ in %) were acquired: SUVmax, SUVpeak, MTV2.5, TLG, ΔSUVmax, ΔSUVpeak, ΔMTV and ΔTLG. Patient characteristics including staging, age, sex, LDH and response evaluation by RECIST were surveyed. Statistical analysis was done using Kaplan-Meier method and Cox regression analysis with respect to OS and PFS.
Results The median follow-up was 9.6 months (2.5–80.5 months). 27 patients were LD and 32 were ED. Forty-six patients (78.0%) had died, and median OS was 8.6 months; 51 patients (86%) showed disease progression, and median PFS was 2.5 months. On univariate analysis, patients with ED, high interval change (ΔSUVmax and ΔSUVpeak) and low PET2 parameters showed longer OS and PFS. Multivariate analyses demonstrated that ΔSUVpeak (HR 2.6, P = 0.002) was an independent prognostic factors for OS, and MTV2.5 of PET2 (HR 2.8, P = 0.001), disease stage (HR 2.7, P = 0.003) and RECIST (HR 2.0, P = 0.023) were independent prognostic factors for PFS.
Conclusions Metabolic and volumetric PET parameters obtained from pre- and post-treatment FDG PET/CT examinations in patients with SCLC have significant prognostic information.

Keywords FDG PET/CT · Small-cell lung cancer · Prognosis · SUVpeak · Treatment response

Introduction

Small-cell lung cancer (SCLC) accounts for ~10–15% of all lung cancers [1]. Generally, SCLC has a more rapid growth time, earlier metastasis and more frequent relapse than non-small-cell lung cancer (NSCLC). It is one of the most aggressive cancers: the median overall survival (OS) is ~12 months, and the median survival without treatment is 2–4 months [1, 2].

SCLC is divided into two stages: limited disease (LD) and extensive disease (ED). LD-SCLC, which is diagnosed in ~30% of patients, is disease confined to one hemithorax encompassed in a radiation port. In contrast, ED-SCLC affects the remaining 70% of patients and extends beyond a single radiation field [3]. Despite its practical usefulness and prognostic advantage, the two-stage system has limitations in terms of accurately reflecting the tumor burden, which is considered a major prognostic factor [4]. Although SCLC is highly responsive to chemotherapy and radiotherapy, many patients relapse early after the end of therapy and exhibit poor long-term survival [5]. Therefore, we need an appropriate tool for accurately predicting recurrence and presenting prognostic

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information about SCLC patients to determine the optimal treatment plan and patient care.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scanning has yielded promising data for the noninvasive staging and management of NSCLC over the past decade [6]. Both the degree of FDG uptake in tumor tissue on PET, as measured using the standardized uptake value (SUV), and the metabolic tumor volume (MTV), defined as the volume of tumor tissue with increased FDG uptake, are important prognostic factors in NSCLC [7, 8]. Previous studies assessed the role of pretreatment ^{18}F-FDG PET/CT in patients with SCLC and confirmed the prognostic value of PET parameters including maximum SUV (SUVmax) and MTV [4, 9–11]. However, few studies have showed correlations between the prognosis and degree of change observed in these parameters in consecutive PET examinations performed before and after treatment. The purpose of this study was to evaluate the prognostic value of metabolic and volumetric parameters in pre- and post-treatment FDG PET examinations of patients with SCLC.

Materials and Methods

Patient Population

This retrospective study was approved by our Institutional Review Board; informed consent was waived. The medical records of 205 patients with SCLC that was initially diagnosed histopathologically between January 2009 and December 2014 were reviewed. Among these, 71 patients underwent two consecutive FDG PET/CT examinations: one for initial staging (PET1) and another for restaging after treatment (PET2). Of these 71 patients, 12 were excluded for the following reasons: 6 patients underwent surgical resection as a treatment for SCLC, and 2 had a history of other malignancies. Additionally, four patients underwent incomplete treatment because of poor general health conditions. Finally, 59 patients diagnosed with SCLC, who received chemotherapy and/or concurrent chemoradiotherapy between two consecutive FDG PET/CT examinations, were included in the analysis. The patients underwent PET2 to evaluate the treatment response a mean 1.2 ± 0.6 months (range: 0.5–2.7 months) after the last day of treatment. The time interval between PET1 and PET2 was 4.8 ± 1.3 months (range: 2.2–7.8 months). Among the 59 patients, 37 (62.7%) received chemotherapy only, and 22 (37.3%) underwent concurrent chemoradiotherapy with or without additional chemotherapy. Most patients received platinum-based chemotherapy; cisplatin plus etoposide was the most common regimen. Among the total 59 patients, 7 underwent prophylactic cranial irradiation (PCI). One patient underwent PCI between PET1 and PET2, and six patients underwent PCI after the PET2 scan. Among 51 patients with disease progression, 44 additionally underwent at least one of the following treatments: chemotherapy, radiation therapy, concurrent chemoradiotherapy and cyberknife surgery for brain metastasis. The Veteran's Administration Lung Group two-stage system, which divides SCLC into LD and ED, was used to define the disease stage.

FDG PET/CT Imaging

^{18}F-FDG was injected intravenously (3.7–5.5 MBq/kg), and scanning began 60 min later. All patients fasted for at least 6 h prior to 18F-FDG PET/CT and had blood glucose levels <170 mg/dl. All data were acquired using a combined PET/CT in-line system (Biograph TruePoint; Siemens Medical Solutions, Knoxville, TN, USA). The CT scan began at the orbitomeatal line and progressed to the proximal thigh (120 kVp, 50 mAs, 5-mm slice thickness) without contrast enhancement, followed by a PET scan over the same body region. The CT data were used for attenuation correction, and the images were reconstructed using a standard ordered-subset expectation maximization (OSEM) algorithm. PET1 and PET2 scans were acquired in the same protocol.

Measurement of PET/CT Parameters and Clinical Data

All PET/CT images were quantified using Mirada XD3 software (Mirada Medical, Oxford, UK). Two experienced nuclear medicine physicians, who were aware of the patients' clinical information, interpreted the PET/CT images by consensus. Regions of interest (ROIs) were placed over the primary lesion and metastatic lymph nodes within the thoracic cavity. The SUVmax, defined as the maximum SUV within the tumor, and average SUV within the 1 cm^3 fixed-sized ROI centered on a high-uptake part of the tumor (SUVpeak) were obtained from the ROI. In addition, a cutoff value of SUV 2.5 was used to measure MTV and total lesion glycolysis (TLG), which is calculated as MTV multiplied by the SUVmean. PET parameters were obtained from PET1 (SUVmax1, SUVpeak1, MTV1 and TLG1) and PET2 (SUVmax2, SUVpeak2, MTV2 and TLG2). In addition, the percent changes between PET1 and PET2 were calculated: ΔSUVmax, ΔSUVpeak, ΔMTV and ΔTLG. The percentage change in SUV between PET1 and PET2 was calculated using the following formula: %ΔSUV = (SUV2 - SUV1)/SUV1 × 100. Patient characteristics including staging, age, sex and serum lactate dehydrogenase (LDH) at initial diagnosis were surveyed. Response Evaluation Criteria in Solid Tumor 1.1 (RECIST1.1) was used to assess the treatment response, and the responses were classified as responder (complete response, CR, or partial response, PR) and non-responder (stable disease, SD, or progressive disease, PD).

Statistical Analysis

Statistical analyses were performed using SPSS software (ver. 24.0; IBM Corp., Armonk, NY, USA). OS and progression-free survival (PFS) were selected as endpoints to evaluate the prognostic value. OS was defined as the time from the date of initial PET/CT to the date of death from any cause or the last clinical follow-up. PFS was defined as the time from the date of initial PET/CT to the first evidence of disease progression evaluated by RECIST. Metabolic parameters obtained from PET1 and PET2 as well as age, gender, stage, LDH and tumor response by RECIST were included in the univariate and multivariate analysis for PFS and OS. All patients were dichotomized into two groups using the median value of all PET parameters and clinical data. The survival time was estimated using the Kaplan-Meier method, and the difference between groups was assessed using log-rank tests. A multiple Cox's proportional hazard model using stepwise forward selection was performed for PET parameters and clinical variables that were significant (P-values <0.05) in the univariate analysis, and the estimated hazard ratio (HR) and 95% confidence interval (CI) were calculated. To avoid multicollinearity between PET parameters, those were classified into three categories, and one representative variable was chosen for multivariate analysis: SUV category (SUVmax, SUVpeak), volume-based category (MTV, TLG) and delta category (ΔSUVmax, ΔSUVpeak and ΔMTV). All tests were two-sided, and P values <0.05 were considered statistically significant.

Results

Patients Characteristics

The patient characteristics, including age, gender, disease stage, LDH, RECIST and treatment, are summarized in Table 1. Of the 59 patients, 39 (66.1%) were male and 20 (33.9%) female, with a median age of 67 years (range: 40–79 years). Based on imaging studies, including FDG PET/CT, enhanced chest CT and brain MRI, 27 (45.8%) patients were classified as LD and 32 (54.2%) as ED. Among 59 patients, 12 (20.3%) showed a normal LDH level (<450 U/l) and 47 (79.7%) showed an elevated LDH level. Among 59 patients, 37 (62.7%) were classified as responder (3 CR, 34 PR) and 22 (37.3%) as non-responder (1 SD, 21 PD).

The median follow-up time was 9.6 months (range: 2.5–80.5 months), and 46 patients (78.0%) patients died. The median OS was 8.6 months (range: 2.5–49 months). Fifty-one patients (86%) experienced disease progression, and the median PFS was 2.5 months (range: 0.4–21.0 months). The median values with range of PET parameters are presented in Table. 2.

Table 1 Patient characteristics (N = 59)

Characteristic	Number of patients (%)
Age	
Median (range)	67 (40–79)
Gender	
Male	39 (66.1)
Female	20 (33.9)
Disease stage	
LD	27 (45.8)
ED	32 (54.2)
LDH	
Normal	12 (20.3)
Elevated	47 (79.7)
RECIST	
Responder	37 (62.7)
Non-responder	22 (37.3)
Treatment	
Chemotherapy	37 (62.7)
CCRT	3 (5.1)
Chemotherapy + CCRT	19 (32.2)

Abbreviations: LD, limited-stage disease; ED, extensive-stage disease; LDH, lactate dehydrogenase; RECIST, response evaluation criteria in solid tumor; CCRT, concurrent chemoradiotherapy

Prognostic Value

Univariate analysis showed that disease stage, ΔSUVmax, ΔSUVpeak, SUVmax2, SUVpeak2, MTV2 and TLG2 were significant predictors of OS (P < 0.05; Table 3). In other words, ED and a high ΔSUVmax, ΔSUVpeak, SUVmax2, SUVpeak2, MTV2 and TLG2 were associated with poor OS (Fig. 1). Similar to OS, many PET parameters obtained from

Table 2 Median values with range of PET parameters

Parameter		Median (range)
PET1	SUVmax1	9.5 (4.7–22.8)
	SUVpeak1	7.9 (3.7–16.1)
	MTV1	131.3 (5.4–1068.9)
	TLG1	592.0 (18.1–5050.6)
PET2	SUVmax2	6.0 (2.5–16.7)
	SUVpeak2	4.2 (2.1–14.2)
	MTV2	9.1 (0.1–192.5)
	TLG2	30.0 (0.3–1465.9)
Change from PET1 to PET2 (%)	ΔSUVmax	−45.2 (−79.2–35.7)
	ΔSUVpeak	−46.8 (−78.0–62.1)
	ΔMTV2.5	−94.4 (−99–345.3)
	ΔTLG	−96.4 (−67.0–88.3)

PET, positron emission tomography; SUVmax, maximum standardized uptake value; SUVpeak, peak standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis

Table 3 Univariate analysis of overall survival and progression-free survival

Parameter		*P*-value	
		OS	PFS
Age	≤67 years vs. >67 years	0.69	0.21
Gender	Male vs. female	0.92	0.46
Disease stage	LD vs. ED	0.04*	<0.001*
LDH	Normal vs. Elevated	0.35	0.027*
RECIST	Responder vs. Non-responder	0.10	<0.001*
SUVmax1	≤9.5 vs. >9.5	0.63	0.21
SUVpeak1	≤7.9 vs. >7.9	0.63	0.21
MTV1	≤132 vs. >132	0.14	<0.001*
TLG1	≤592 vs. >592	0.19	<0.002*
SUVmax2	≤6 vs. >6	0.005*	<0.001*
SUVpeak2	≤4.2 vs. >4.2	0.017*	0.031*
MTV2	≤9.1 vs. >9.1	0.018*	<0.001*
TLG2	≤30 vs. >30	0.01*	0.001*
ΔSUVmax (%)	≤ −45.2 vs. > −45.2	0.004*	0.003*
ΔSUVpeak (%)	≤ −46.8 vs. > −46.8	0.001*	<0.001*
ΔMTV2.5 (%)	≤ −94.4 vs. > −94.4	0.18	0.025*
ΔTLG (%)	≤ −96.4 vs. > −96.4	0.11	0.07

OS, overall survival; PFS, progression-free survival; LDH, lactate dehydrogenase; RECIST, response evaluation criteria in solid tumor; SUVmax, maximum standardized uptake value; SUVpeak, peak standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis

*Statistically significant

PET1 and PET2 were significant predictors of PFS in univariate analysis ($P < 0.05$; Fig. 2).

In each category of PET parameter, one representative variable was selected for the following reasons. In the SUV catergory, we chose SUVpeak based on the fact that SUVpeak is less affected by noise than SUVmax. In the volume-based category, because TLG is calculated using both MTV and SUVmean (TLG = MTV * SUVmean), we chose MTV instead of TLG. Lastly, in the delta category, we selected ΔSUVpeak considering that SUVpeak is less affected by noise than SUVmax and that ΔMTV was not a prognostic factor of OS in univariate analysis. No strong correlation was found between variables in the correlation analysis (absolute coefficient value <0.7).

In multivariate analysis, the only independent prognostic factor that correlated with OS was ΔSUVpeak (HR 2.6, $P = 0.002$, Table 4). A high disease stage (HR 2.7, $P = 0.003$), non-responders evaluated by RECIST (HR 2.0, $P = 0.023$) and high MTV2 (HR, 2.8, $P = 0.001$) were independent prognostic factors for poor PFS.

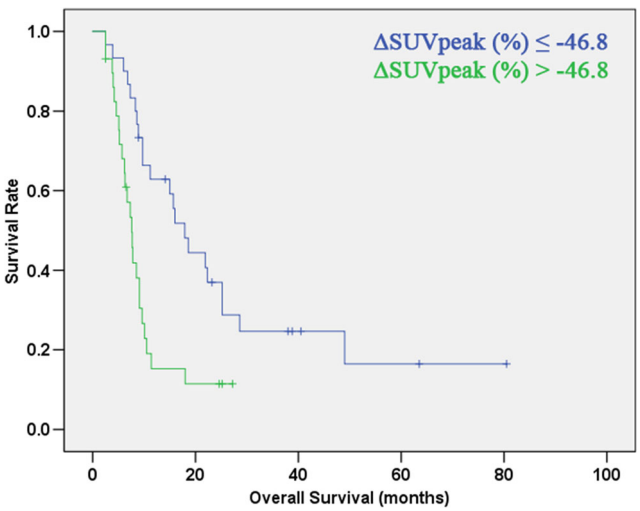

Fig. 1 Kaplan-Meier overall survival curves according to ΔSUVpeak (%). A marked interval reduction in SUVpeak was significantly associated with a longer OS ($P = 0.001$)

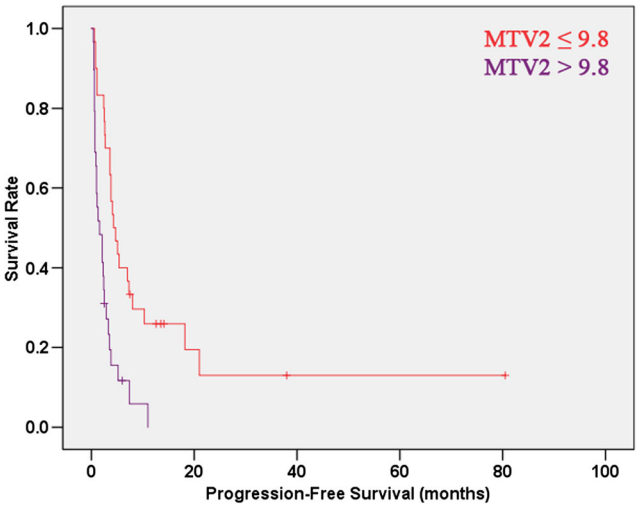

Fig. 2 Kaplan-Meier progression-free survival curves of patients according to metabolic tumor volume (MTV2). A low MTV2 was significantly associated with a longer PFS ($P < 0.001$)

Table 4 Multivariate analysis of overall survival and progression-free survival

	OS			PFS		
Parameters	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Disease stage				2.7	1.4–5.3	0.003*
RECIST				2.0	1.1–3.7	0.023*
MTV2				2.8	1.5–5.2	0.001*
ΔSUVpeak (%)	2.6	1.4–4.8	0.002*			

OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumor; SUVpeak, peak standardized uptake value; MTV, metabolic tumor volume; HR, hazard ratio; CI, confidence interval

*Statistically significant

Discussion

This study compared FDG PET parameters obtained from two consecutive FDG PET/CT scans performed before and after treatment in a relatively large number of SCLC patients from a single institution, to predict prognosis. The results showed a large reduction in SUVpeak following treatment was an important independent prognostic factor for overall survival, and remnant tumor volume was associated with a longer progression-free survival.

In many malignant tumors, conventional CT scans are routinely used to monitor the response to treatment. However, criteria for response by CT scans is based on size and do not provide tumor metabolic information. Differentiating between necrotic or fibrous tissue and residual disease is challenging with post-therapy imaging. Metabolic cellular changes are known to precede tumor regression [12], which makes it possible for FDG PET/CT to reflect early changes in the metabolic behavior of malignancies. FDG PET/CT can yield several PET parameters that are used to quantitatively measure tumor FDG uptake. SUVmax is a widely used quantitative parameter because of its simplicity and convenience, but it has the disadvantage of vulnerability to image noise [13]. SUVpeak has the advantage of being less affected by image noise than SUVmax [14, 15]. In the current study, we investigated the feasibility of prognostic imaging biomarkers with the above-mentioned parameters.

Several studies have shown that tumors with high SUV values in FDG PET/CT are associated with a poor prognosis in patients with various malignancies, including head-and-neck cancer, colorectal cancer, pancreatic cancer and NSCLC [16–19]. However, little evidence has been presented regarding the role of FDG PET/CT in SCLC patients. Although tumor stage is the most important prognostic factor to date, further stratification of patients within the same stage into distinct survival groups is needed. For these reasons, several SCLC studies have attempted to evaluate the prognostic value of FDG PET/CT. Many of these suggested that tumor metabolic parameters, such as SUVmax, MTV and TLG, are associated with patient prognosis [4, 9, 11, 20, 21]. In contrast, other studies have not proved that PET parameters are independent prognostic factors for SCLC patients when evaluated using pretreatment FDG PET/CT alone [22, 23]. Comparing two FDG PET/CT scans performed before and after the treatment, a group of investigators in Japan demonstrated that FDG PET/CT has a potential role in identifying the therapeutic response of SCLC patients [24]. However, their study enrolled only 12 SCLC patients, and they focused on the role of FDG PET/CT for early response assessment without survival analysis.

In the present study, survival analysis was done using multiple PET parameters from two consecutive FDG PET/CT scans performed before and after treatment. The results of this study could explain why some previous data failed to show the prognostic value of pretreatment FDG PET/CT in SCLC. Although most SCLC patients respond to initial chemotherapy, those with disease progression (chemoresistance group) at the first response assessment have inferior outcomes (Figs. 3, 4). It may be that the change from baseline to after therapy is more important than the baseline PET finding alone. While tumor response by the RECIST criteria (responder vs. non-responder) was not an independent prognostic factor regarding OS, change of SUVpeak following treatment better reflected the overall survival of patients. The PET parameters from single time point scans and clinical variables were not independent prognostic factors for OS.

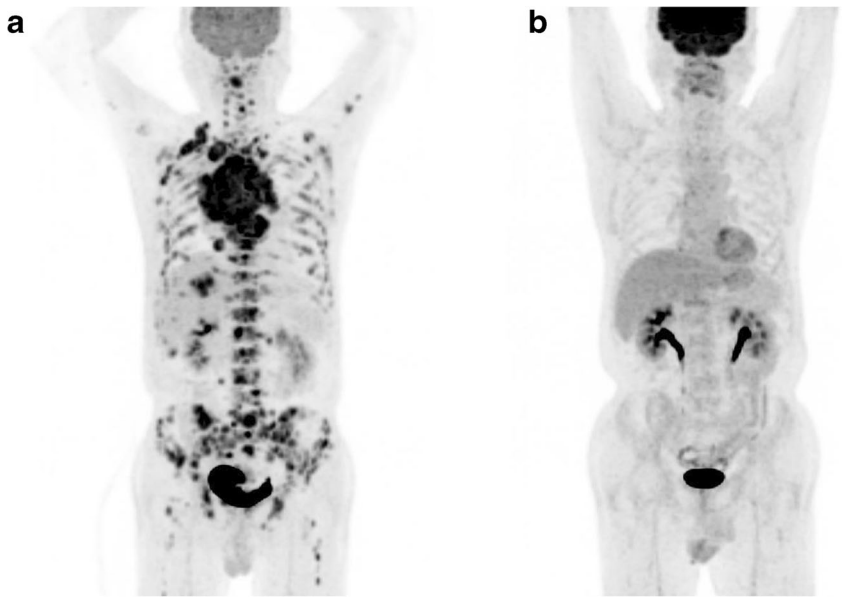

Fig. 3 A 63-year-old male with extensive disease (ED) who received cisplatin and etoposide chemotherapy. Comparing pretreatment ^{18}F-fluorodeoxyglucose PET/computed tomography (FDG PET/CT) **(a)** and post-treatment PET **(b)**, the peak standardized uptake value (ΔSUVpeak) (%) was −69.9%. Progression-free survival (PFS) was 10.3 months, and the patient was still alive at the end of the study

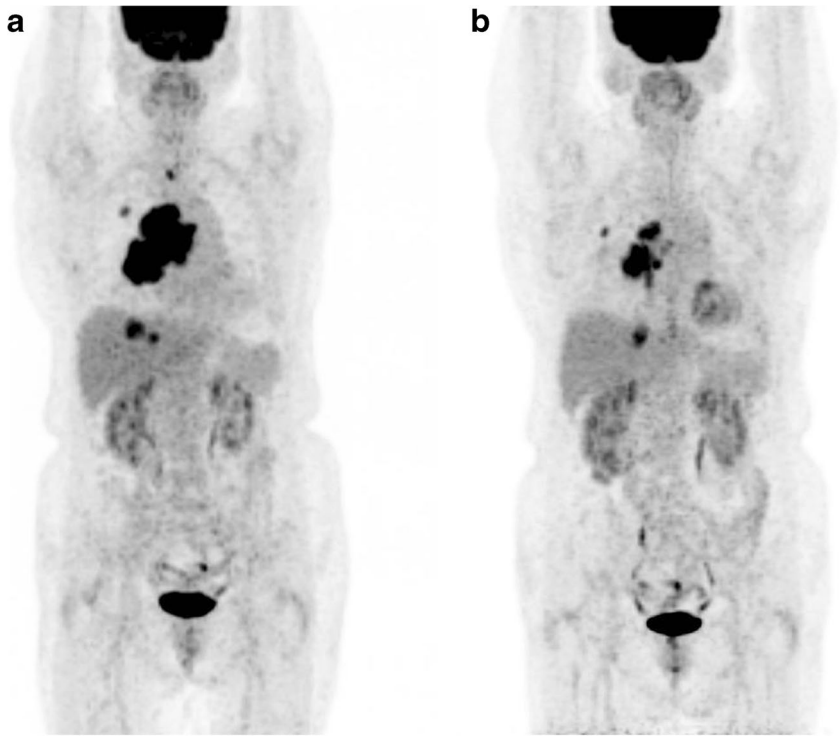

Fig. 4 A 76-year-old female with ED who received cisplatin and etoposide chemotherapy. Comparing pretreatment FDG PET/CT **(a)** and post-treatment PET **(b)**, the ΔSUVpeak (%) was −16.1%. OS and PFS were 3.8 and 2.1 months, respectively

Although more evidence has to be accumulated and consensus about the cutoff value has to be reached, in clinical practice, patients with insignificant changes in SUVpeak between two consecutive PET scans would be classified into the chemoresistance group, and more aggressive treatment or an earlier change of chemotherapy regimen could be applied.

For PFS, MTV from post-treatment PET (MTV2) was the only independent prognostic factor among the PET parameters, in addition to stage and RECIST response. Although we failed to prove that MTV2 was an independent prognostic factor for OS, MTV2 was a significant predictor by univariate analysis. The remaining metabolic tumor burden after treatment best reflects the chemoresistant portion of the tumor and is probably related to progression-free survival. Interestingly, none of the PET parameters from pretreatment PET predicted the prognosis of SCLC patients independently. Compared with previous studies showing that PET parameters from pretreatment PET were good predictors for prognosis [11, 20], this discrepant result is thought to be due to the relatively small number of patients and different study designs and clinical settings including the treatment protocol. A prospective study with a larger number of patients is required for further valiadation of the association between these PET parameters and prognosis in SCLC patients.

There were some limitations to the current study. It is a retrospective study with intrinsic bias regarding heterogeneity in terms of the patient selection, treatment protocol and timing of PET/CT scanning. Here, we only measured volumetric PET parameters for intrathoracic tumors. One previous study showed that determining the whole-body metabolic tumor volume (WBMTV) using ^{18}F-FDG PET is an independent prognostic factor for survival in patients with SCLC [20]. Although evaluating WBMTV could reflect the true systemic tumor burden, it would be challenging to measure volumetric PET parameters in extrathoracic lesions using a threshold-based cutoff SUV after delineating the boundaries of the lesions and excluding physiologic activity. Furthermore, measurement of PET parameters, including complete lesions, is very time-consuming, not feasible during routine clinical practice [11], and is subject to inter- and intra-reader variability. Some studies used an ROI placed over the primary SCLC lesion without metastatic lymph nodes. Because primary lesions are conglomerated with adjacent metastatic lymph nodes in many cases of SCLC, it is challenging and often not possible to obtain an accurate ROI of the primary lesion. In the present study, MTV2.5 obtained from post-treatment FDG PET/CT was an independent prognostic factor for PFS. This suggests that only measuring the metabolic burden of the intrathoracic tumor could give sufficient information about disease progression without measuring the WBMTV. When the SUVmax was measured for all tumors of the whole body, 7 out of 59 patients had a higher SUV in the extrathoracic tumor than in the intrathoracic tumor. However, applying the higher SUV from the extrathoracic tumor did not change the results from univariate and multivariate analyses.

Despite these limitations, our study is meaningful because it is the first to evaluate whether changes in the PET parameters after treatment are prognostic factors for SCLC patients.

Performing a prospective study with a larger population adding the TNM staging and other PET response criteria (PERCIST or EORTC) is required to validate the results of our study. In addition, we plan to investigate whether an appropriate cutoff for changes in PET parameters could be applied in clinical practice.

Conclusions

In conclusion, this study demonstrated that the percent change in SUVpeak from pre- to post-treatment FDG PET/CT examinations was an independent prognostic factor for OS in patients with SCLC. In addition, MTV2.5 from post-treatment FDG PET/CT was an independent prognostic factor for PFS. In other words, marked interval reductions in the SUVpeak and remnant MTV after treatment are favorable prognostic factors. The ^{18}F-FDG PET/CT findings help identify patients who have unfavorable prognostic factors, which will make it possible to provide intensive therapy and optimal patient care to achieve a better prognosis.

Compliance with Ethical Standards

Conflict of Interest Hyoungwoo Kim, Ie Ryung Yoo, Sun Ha Boo, Hye Lim Park, Joo Hyun O and Sung Hoon Kim declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

For this type of study, formal consent is not required.

Informed Consent The Institutional Review Board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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