FULL PAPER

Prognostic value of fluorine-18 fludeoxyglucose positron emission tomography parameters differs according to primary tumour location in small-cell lung cancer

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Objective: To investigate the prognostic value of fluorine-18 fludeoxyglucose (FDG) positron emission tomography (PET) parameters for small-cell lung cancer (SCLC), according to the primary tumour location, adjusted by conventional prognostic factors.
Methods: From 2008 to 2013, we enrolled consecutive patients with histologically proven SCLC, who had undergone FDG-PET/CT prior to initial therapy. The primary tumour location was categorized into central or peripheral types. PET parameters and clinical variables were evaluated using univariate and multivariate analysis.
Results: A total of 69 patients were enrolled in this study; 28 of these patients were categorized as having the central type and 41 patients as having the peripheral type. In univariate analysis, stage, serum neuron-specific enolase, whole-body metabolic tumour volume (WB-MTV) and whole-body total lesion glycolysis (WB-TLG) were

found to be significant in both types of patients. In multivariate analysis, the independent prognostic factor was found to be stage in the central type, but WB-MTV and WB-TLG in the peripheral type. Kaplan–Meier analysis demonstrated that patients with peripheral type with limited disease and low WB-MTV or WB-TLG showed significantly better overall survival than all of the other groups ($p < 0.0083$).
Conclusion: The FDG-PET volumetric parameters were demonstrated to be significant and independent prognostic factors in patients with peripheral type of SCLC, while stage was the only independent prognostic factor in patients with central type of SCLC.
Advances in knowledge: FDG-PET is a non-invasive method that could potentially be used to estimate the prognosis of patients, especially those with peripheral-type SCLC.

INTRODUCTION

Small-cell lung cancer (SCLC) is one of the most aggressive cancers with frequent recurrence, even after an initial favourable response to cytotoxic treatments. In the USA, despite the development of radical therapies, 5-year survival remains at 20–25% for limited disease (LD) and 5% for extensive disease (ED).[1] Several prognostic factors for SCLC have previously been reported including stage, age, sex, performance status (PS) and serum lactate dehydrogenase (LDH).[2–5] Among them, clinical stage is regarded as the main prognostic factor in clinical practice. No other factor has been well investigated, which could be a potential trigger for subdividing SCLC and existing therapies, although other clinical indices such as age and PS are often referred to in deciding the therapy regimen.

[18]F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT-based imaging parameters such as maximum standardized uptake value (SUV_{max}), metabolic tumour volume (MTV) and total lesion glycolysis (TLG) have been suggested as prognostic factors for various neoplasms.[6–9] As for SCLC, only a small number of studies have investigated the relationship between FDG-PET/CT parameters and prognosis.[10–12] They regarded whole-body metabolic tumour volume (WB-MTV) as one of the important prognostic factors; however, this has not been well established.

The standard therapy regimens for SCLC have not changed in a long time. This may be because the pathological diagnosis of SCLC is usually sufficient with electroscopic observation. Special immunohistochemical staining is

sometimes required but not always necessary, whereas many driver mutations have been detected and surveyed routinely for non-small-cell cancer, especially for adenocarcinoma; this has helped improve prognosis dramatically in some cases. The possible biological difference between centrally and peripherally located SCLC has been discussed in a few articles.[13–15] For example, it has been pointed out that hilar nodes in SCLC tend to be involved early and massively, when the primary lesion is located in the peripheral lung parenchyma.[13] However, differences in prognosis according to tumour location remain controversial.[14,16,17] Although pathological differences have not yet been well established, FDG-PET/CT can supposedly be a helpful tool in observing tumour characteristics and prognosis non-invasively, especially SCLC, where surgery is usually not indicated and direct observation of the entire tumour is unachievable.

The aim of the present study was to investigate the prognostic value of FDG-PET parameters such as SUV_{max}, WB-MTV and whole-body total lesion glycolysis (WB-TLG) for SCLC, according to the primary tumour location, adjusted by those of conventional prognostic factors in patients with SCLC.

METHODS AND MATERIALS
Patients
From January 2008 to December 2013, a total of 112 consecutive patients who were pathologically diagnosed with SCLC at Kyoto University Hospital were enrolled in the study. We included the patients who had undergone pre-treatment FDG-PET/CT, followed by treatment with at least one course of standard chemotherapy at our institution. The exclusion criteria were combined SCLC and coexisting malignancy. 43 patients were excluded based on the criteria as follows: 39 patients had no PET/CT prior to initial therapy; 3 patients were diagnosed as having combined SCLC; and the remaining 1 patient had coexisting oesophageal cancer. In total, 69 patients (male : female ratio, 57 : 12; median age, 75 years; range, 56–86 years) were eligible for the study.

This retrospective study was approved by the institutional review board, and written informed consent was obtained from each patient regarding access of their data.

Positron emission tomography/CT image acquisition
PET/CT scanning was performed using a combined PET/CT scanner [Discovery ST Elite, GE Healthcare, Waukesha, WI ($n = 11$); Biograph™ 16 TruePoint™, Siemens Healthcare, Erlangen, Germany ($n = 28$); Biograph™ 64 TruePoint™, Siemens Healthcare ($n = 30$)]. We confirmed that each scanner underwent routine maintenance using a consistent cross-calibration factor with an error of <5%. All patients fasted for ≥4 h before the administration of FDG. The plasma glucose level at the time of FDG injection was confirmed to be <200 mg dl^{-1} in all patients. PET emission data acquisition commenced at 71.8 ± 14.8 (mean ± SD) min after injection of a dose of 3.7–4.5 MBq kg^{-1} of FDG; a whole-body scan was conducted starting at the level of the thigh and extending to the head. CT scans were acquired for the same coverage with a range of 20–120 mAs of current–time product. The PET images obtained were reconstructed with CT-derived attenuation correction using the iterative reconstruction algorithm.

Measurements of positron emission tomography/CT parameters
The PET images were displayed on a workstation (Advantage Workstation, v. 4.4: GE Healthcare, Waukesha, WI). The outcome of the patients was not disclosed to the observers. Each tumour was examined with a sphere-shaped volume of interest (VOI) that included the entire lesion in the axial, sagittal and coronal planes. The brain was excluded from the calculation because reliability would be decreased, as a result of the high physiological uptake in the background tissue. With the use of CT images, FDG uptake in the normal organs such as the cardiac muscle, bowel, stomach, liver and urinary tract was carefully excluded from the VOI. The maximum standardized uptake value of the primary tumour (P-SUV_{max}), the highest value of the maximum standardized uptake value among the primary and metastatic disease (H-SUV_{max}), WB-MTV and WB-TLG were measured for each case. The SUV_{max} of the VOI was calculated as follows: (decay-corrected activity/tissue volume)/(injected dose/body weight). WB-MTV was defined as total whole-body tumour volume with a cut-off of ≥40% of the H-SUV_{max}. The cut-off value was determined by referring to data reported in previous studies.[18–23] Each VOI for calculating MTV and TLG was first placed manually, paying careful attention not to include high physiological uptake, and then MTV

Figure 1. Representative cases of the central type (a) and peripheral type (b) on CT images. The primary tumour is delineated with a thin black line. The transparent grey circle demonstrates a region 2 cm from the origin of the nearest segmental bronchus. If the margin of the primary tumour is within the circle, it is classified as a central type.
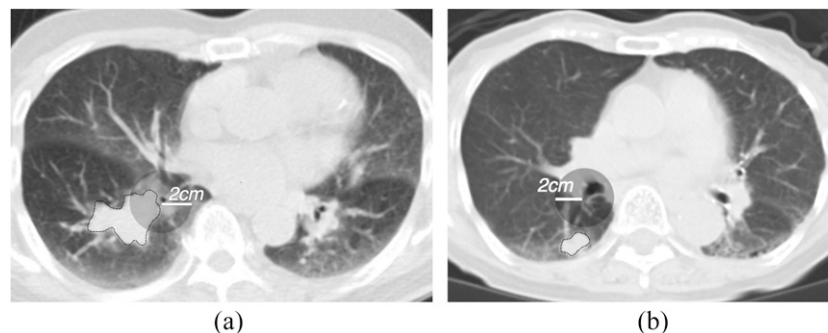

(a)   (b)

Table 1. Patient characteristics

Variables	Total ($n = 69$)	Central ($n = 28$)	Peripheral ($n = 41$)	p-value
Age				
Mean ± SD	73.9 ± 8.2	76.0 ± 8.3	72.4 ± 7.9	0.036[a]
Median	75	78	72	
Gender				
Male	57	23	34	1.00
Female	12	5	7	
Smoking index				
Mean ± SD	1297 ± 1803	1675 ± 2735	1039 ± 558	0.076
Median	960	1010	960	
ECOG PS				
0 or 1	62	25	37	1.00
2 or 3	7	3	4	
LDH [normal: 129–241 (IU/l)]				
Mean ± SD	247.6 ± 95.8	273 ± 131.3	230.3 ± 56.4	0.034[a]
Median	223	250.5	214	
Tumour markers				
NSE [normal <12 (ng ml^{-1})]				
Mean ± SD	50.4 ± 74.1	74.9 ± 100.8	33.3 ± 40.9	0.11
Median	22.4	31.7	20.9	
ProGRP [normal <70 pg ml^{-1})]				
Mean ± SD	996 ± 3118	1630 ± 4554	562 ± 435	0.082
Median	135	407	122	
CYFRA [normal <2.2 ng ml^{-1})]				
Mean ± SD	3.59 ± 2.55	3.06 ± 1.50	3.94 ± 3.02	0.92
Median	3	2.7	3.05	
CEA [normal <5 (ng ml^{-1})]				
Mean ± SD	21.7 ± 70.3	30.6 ± 94.8	15.7 ± 47.4	0.2
Median	4.5	5.4	4.5	
Stage				
Limited disease	38	14	24	0.62
Extensive disease	31	14	17	
Therapy				
Chemoradiotherapy	27	14	13	0.14
Chemotherapy	42	14	28	
P-SUV$_{max}$ [g ml^{-1}]				
Mean ± SD	9.86 ± 5.46	11.74 ± 5.77	8.61 ± 4.93	0.0098[a]
Median	9.75	10.6	9.3	
H-SUV$_{max}$ [g ml^{-1}]				
Mean ± SD	11.69 ± 4.63	12.21 ± 5.52	11.32 ± 3.95	0.22
Median	11.6	11.65	11.5	

(Continued)

Table 1. (Continued)

Variables	Total ($n = 69$)	Central ($n = 28$)	Peripheral ($n = 41$)	*p*-value
WB-MTV [cm^3]				
Mean $\pm$ SD	72.6 $\pm$ 82.1	100.6 $\pm$ 93.6	53.4 $\pm$ 68.1	0.018[a]
Median	43.9	74.0	38.3	
WB-TLG [g]				
Mean $\pm$ SD	568.6 $\pm$ 771.2	823.6 $\pm$ 915.6	394.5 $\pm$ 607.2	0.022[a]
Median	336.1	607.6	226.3	

CEA, carcinoembryonic antigen; CYFRA, cytokeratin 19 fragment; ECOG, Eastern Cooperative Oncology Group; H-SUV$_{max}$, maximum standardized uptake value of the highest lesion of the disease; IU, international unit; LDH, lactate dehydrogenase; NSE, neuron-specific enolase; ProGRP, pro-gastrin-releasing peptide; PS, performance status; P-SUV$_{max}$, maximum standardized uptake value of the primary tumour lesion; SD, standard deviation; WB-MTV, whole-body metabolic tumour volume; WB-TLG, whole-body total lesion glycolysis.
The paired *t*-test was used for the evaluation of age, smoking index, LDH, tumour markers, maximum of standardized uptake value, MTV and TLG. Fisher's exact test was used for the evaluation of sex, performance status, stage and therapy.
[a]$p < 0.05$.

was automatically extracted on a workstation. The summed MTV was produced as the WB-MTV. The WB-TLG was calculated as the sum of the product of mean standardized uptake value and the MTV of each lesion.

Primary tumour location
The primary tumour locations were categorized into two types: the central type and peripheral type. Because in SCLC the border of these two types has not been fully established using CT, the tumour location was defined according to one of the criteria used for non-small-cell lung cancer (NSCLC).[24] If the tumour margin was <2 cm from the regional segmental bronchi, the tumour was defined as a central type (Figure 1).

The location of the primary tumour was judged using the pre-treatment CT images. If a conventional chest CT scan was unavailable, CT images from the PET/CT scan were evaluated. All images were anonymized and blindly evaluated by two board-certified radiologists (TN and SK). The interreader variability in the location of the primary tumour assessed by the two readers was evaluated using κ statistics. κ values of >0.8, 0.6–0.8, 0.4–0.6 and <0.4 were regarded as excellent, good, moderate and poor, respectively. The discordant cases were consensually determined by discussion between both readers and a third reader, who was a chest radiology expert with 20 years' experience.

Clinical indices
For all patients, staging was performed using the initial PET/CT and contrast-enhanced brain MRI, with the exception of one patient who did not undergo brain MRI because he had already been diagnosed with ED with PET/CT. The Veterans Administration staging system was applied for disease staging;[25] namely LD was defined as disease confined to the ipsilateral hemithorax, ipsilateral hilum, bilateral mediastinum and subclavian areas. The disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion and haematogenous metastasis, was categorized as ED. Other clinical indices including age, sex, smoking index (multiplication of the number of consumed cigarettes per day by the number of years of smoking) and laboratory

data regarding blood tests [serum LDH, neuron-specific enolase (NSE), pro-gastrin-releasing peptide (ProGRP), cytokeratin 19 fragment (CYFRA) and carcinoembryonic antigen (CEA)] were obtained from the most recent records prior to PET/CT.

Statistical analysis
For both the central and peripheral types, the patient population was subdivided by the median values of the PET/CT parameters (P-SUV$_{max}$, H-SUV$_{max}$, WB-MTV and WB-TLG), together with the following clinical characteristics that have been demonstrated to be prognostic factors: age; sex; smoking index; Eastern Cooperative Oncology Group PS; clinical stage; type of therapy; and serum LDH. Tumour markers, namely NSE, ProGRP, cytokeratin 19 fragment and CEA, were also included in the analyses. Progression-free survival (PFS) was calculated as the interval from the initial PET/CT study to any recurrence or last follow-up. Overall survival (OS) was assessed from the initial PET/CT date to death or last follow-up. The association between patient outcome and the factors listed above was examined using the univariate Cox proportional hazards model. Multivariate analysis was performed by means of a Cox proportional hazard model using PET/CT parameters and clinical variables with *p*-values <0.02 in the univariate analysis. PFS and OS curves were plotted using Kaplan–Meier methods, and survival differences between the groups were assessed using the log-rank test. A two-sided *p*-value of <0.05 was considered to indicate statistical significance. Bonferroni correction was adopted, if multiple statistical tests were performed simultaneously on a single data set. All statistical analyses were performed using JMP® pro 11 software (SAS® Institute Inc., Cary, NC).

RESULTS
Patients
The characteristics of the patients are listed in Table 1. Of the 69 patients, 27 patients had undergone chemoradiotherapy, while 42 patients had undergone chemotherapy only. The first-line chemotherapy regimens were as follows: cisplatin plus etoposide ($n = 29$); cisplatin plus irinotecan ($n = 4$); carboplatin plus etoposide ($n = 33$); and carboplatin plus irinotecan ($n = 3$).

Table 2. Univariate Cox proportional hazard models for overall survival (OS) and progression-free survival (PFS)

Variables	PFS		OS	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Central type ($n = 28$)				
Age	2.67 (1.08–6.38)	0.034[a]	3.19 (1.11–10.49)	0.031[a]
Gender (M : F)	1.37 (0.51–4.75)	0.56	4.04 (0.80–73.50)	0.10
Smoking index	0.85 (0.36–2.00)	0.71	0.74 (0.27–2.03)	0.55
ECOG PS	1.83 (0.42–5.80)	0.38	0.98 (0.053–5.29)	0.99
Serum LDH	1.93 (0.83–4.73)	0.13	3.29 (1.15–10.69)	0.026
Tumour markers				
NSE	3.25 (1.36–8.18)	0.0084[b]	3.86 (1.35–12.59)	0.012[b]
ProGRP	1.67 (0.70–4.17)	0.25	1.53 (0.53–4.70)	0.43
CYFRA	0.84 (0.35–2.01)	0.69	0.55 (0.17–1.55)	0.26
CEA	2.04 (0.84–5.03)	0.12	4.51 (1.48–15.41)	0.0082
Stage	5.37 (2.01–16.06)	0.0007[b]	30.01 (5.62–557.55)	<0.0001[b]
Therapy	4.94 (1.84–14.80)	0.0013[b]	15.73 (4.02–104.42)	<0.0001[b]
P-SUV$_{max}$	1.00 (0.41–2.39)	1	0.98 (0.36–2.69)	0.97
H-SUV$_{max}$	1.04 (0.43–2.48)	0.930	1.15 (0.42–3.15)	0.78
WB-MTV	3.93 (1.62–10.21)	0.0024[b]	5.31 (1.78–19.44)	0.0024[b]
WB-TLG	3.11 (1.29–7.85)	0.011[b]	5.18 (1.73–19.00)	0.0028[b]
Peripheral type ($n = 41$)				
Age	1.74 (0.86–3.53)	0.12	1.54 (0.68–3.51)	0.2
Gender (M : F)	2.29 (0.87–7.92)	0.097	2.89 (0.96–12.38)	0.061
Smoking index	1.10 (0.54–2.22)	0.79	1.43 (0.62–3.31)	0.4
ECOG PS	1.77 (0.52–4.60)	0.32	1.44 (0.34–4.25)	0.57
Serum LDH	1.24 (0.62–2.49)	0.55	1.62 (0.72–3.88)	0.25
Tumour markers				
NSE	2.65 (1.26–5.78)	0.01[b]	3.98 (1.57–11.48)	0.0031[b]
ProGRP	1.28 (0.64–2.59)	0.49	1.12 (0.50–2.60)	0.79
CYFRA	1.15 (0.58–2.30)	0.68	0.86 (0.37–1.94)	0.72
CEA	1.16 (0.57–2.37)	0.68	1.37 (0.61–3.21)	0.45
Stage	3.54 (1.66–7.72)	0.0012[b]	6.27 (2.49–17.95)	<0.0001[b]
Therapy	1.99 (0.95–4.56)	0.069	1.85 (0.76–5.16)	0.18
P-SUV$_{max}$	1.65 (0.82–3.36)	0.16	1.86 (0.82–4.39)	0.14
H-SUV$_{max}$	1.82 (0.91–3.73)	0.090	2.27 (0.99–5.65)	0.052
WB-MTV	5.21 (2.35–12.51)	<0.0001[b]	8.16 (2.95–28.98)	<0.0001[b]
WB-TLG	4.98 (2.23–11.98)	<0.0001[b]	8.02 (2.89–28.53)	<0.0001[b]

CEA, carcinoembryonic antigen; CI, confidence interval; CYFRA, cytokeratin 19 fragment; ECOG, Eastern Cooperative Oncology Group; F, female; H-SUV$_{max}$, maximum standardized uptake value of the highest lesion of the disease; LDH, lactate dehydrogenase; M, male; NSE, neuron-specific enolase; ProGRP, pro-gastrin-releasing peptide; PS, performance status; P-SUV$_{max}$, maximum standardized uptake value of the primary tumour lesion; WB-MTV, whole-body metabolic tumour volume; WB-TLG, whole-body total lesion glycolysis.
[a]$p < 0.05$.
[b]$p < 0.02$.

4 out of 38 patients with LD (including 1 patient with central type and 3 patients with peripheral type) and 7 out of 31 patients with ED (including 4 patients with central type and 3 patients with peripheral type) were unable to complete fist-line chemotherapy because of toxicity. Radiation therapy was administered concurrently at a total dose of 44–60 Gy to the chest area, when

Table 3. Multivariate Cox proportional hazard models for overall survival (OS) and progression-free survival (PFS)

Variables	PFS		OS	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Central type (*n* = 28)				
Stage	4.43 (1.42–15.00)	0.01[a]	26.05 (4.28–509.30)	<0.0001[a]
NSE	2.30 (0.86–6.55)	0.10	2.03 (0.59–7.97)	0.27
P-SUV$_{max}$	1.06 (0.39–2.86)	0.900	1.07 (0.34–3.43)	0.90
Stage	4.14 (1.47–12.97)	0.0068[a]	24.86 (4.34–475.1)	<0.0001[a]
NSE	2.60 (0.95–7.38)	0.062	2.19 (0.63–8.45)	0.22
H-SUV$_{max}$	0.76 (0.29–1.96)	0.56	0.89 (0.29–2.86)	0.85
Stage	4.04 (1.41–12.80)	0.0091[a]	23.44 (3.97–453.6)	<0.0001[a]
NSE	0.87 (0.19–5.57)	0.88	0.36 (0.047–4.56)	0.39
WB-MTV	3.25 (0.51–18.25)	0.21	7.90 (0.55–83.08)	0.12
Stage	3.91 (1.33–12.58)	0.013[a]	23.35 (3.88–453.54)	<0.0001[a]
NSE	1.92 (0.64–5.73)	0.24	1.14 (0.25–5.90)	0.87
WB-TLG	1.60 (0.51–4.91)	0.42	2.60 (0.49–14.10)	0.26
Peripheral type (*n* = 41)				
Stage	2.39 (0.76–8.65)	0.14	5.99 (1.37–40.16)	0.015[a]
NSE	1.48 (0.45–4.36)	0.51	1.13 (0.19–5.45)	0.89
P-SUV$_{max}$	1.18 (0.54–2.59)	0.68	0.86 (0.33–2.30)	0.76
Stage	2.33 (0.82–7.80)	0.12	5.09 (1.25–29.99)	0.021[a]
NSE	1.48 (0.46–4.25)	0.50	1.09 (0.20–5.02)	0.92
H-SUV$_{max}$	1.47 (0.72–3.08)	0.29	1.43 (0.58–3.75)	0.44
Stage	1.31 (0.45–4.44)	0.64	2.85 (0.77–14.43)	0.12
NSE	0.94 (0.30–2.85)	0.92	0.49 (0.10–2.52)	0.49
WB-MTV	4.39 (1.40–14.13)	0.011[a]	6.85 (1.30–36.71)	0.023[a]
Stage	1.30 (0.44–4.53)	0.66	2.84 (0.77–14.70)	0.13
NSE	0.96 (0.30–2.91)	0.94	0.49 (0.10–2.56)	0.39
WB-TLG	4.15 (1.24–13.79)	0.021[a]	6.75 (1.20–36.86)	0.031[a]

CI, confidence interval; H-SUV$_{max}$, maximum standardized uptake value of the highest lesion of the disease; NSE, neuron-specific enolase; P-SUV$_{max}$, maximum standardized uptake value of the primary tumour lesion; WB-MTV, whole-body metabolic tumour volume; WB-TLG, whole-body total lesion glycolysis.
[a]$p < 0.05$.

the disease was limited to the tolerable radiation field. Six patients with LD underwent total excision of the tumour without pre-operative pathological diagnosis. After diagnosis as SCLC using tumour specimens, patients received adjuvant therapy (definitive chemoradiotherapy and chemotherapy was performed for two and four patients, respectively). 10 patients (including 7 patients with central type and 3 patients with peripheral type) had brain metastases before the initial treatment. The median follow-up period was 21.8 months (range, 2.3–68.5 months). There were 16 survivors during the study period.

Subgroups of the central and peripheral types
The reproducibility in identifying the primary tumour location was good (as $\kappa = 0.67$). After discussion between the two CT readers and the chest radiology expert, 28 patients were categorized as having the central type and 41 patients as having the peripheral type. Age ($p = 0.036$), serum LDH ($p = 0.034$), P-SUV$_{max}$ ($p = 0.0098$), WB-MTV ($p = 0.018$) and WB-TLG ($p = 0.022$) of the central type were significantly higher than those of the peripheral type (Table 1).

Univariate survival analysis
Univariate analysis for PFS and OS was performed according to the median values for the following clinicolaboratory characteristics: age; Eastern Cooperative Oncology Group PS; LDH level; stage; and tumour markers (Table 2). Among them, ED, high NSE level, high WB-MTV and WB-TLG led to significantly worse prognosis regarding PFS and OS for both the central and

Figure 2. Hazard ratio of progression-free survival (PFS) (a) and overall survival (OS) (b) using positron emission tomography (PET) parameters. Forest plots describe the hazard ratio regarding the central and peripheral types. PET/CT volumetric parameters such as whole-body metabolic tumour volume and whole-body total lesion glycolysis are independent prognostic factors only in the peripheral type. CI, confidence interval; H-SUV$_{max}$, maximum standardized uptake value of the highest lesion of the disease; MTV, metabolic tumour volume; P-SUV$_{max}$, maximum standardized uptake value of the primary tumour lesion; TLG, total lesion glycolysis.
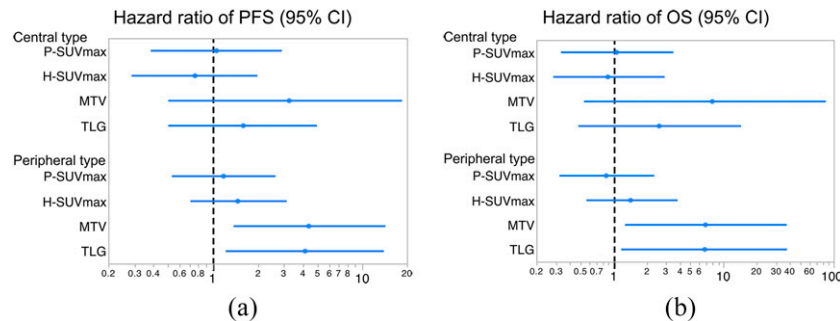
peripheral types. Old age was a significant prognostic factor only in the central type. High LDH and CEA level led to a significantly worse prognosis only regarding OS in the central type. All of the other parameters showed no statistical significance in terms of prognosis.

Multivariate survival analysis

To assess the possible independent effects of the PET/CT parameters, multivariate analyses were performed regarding PFS and OS adjusted for stage and serum NSE, both of which showed p-values of <0.02 in the univariate analyses (Table 3). In the peripheral type, WB-MTV and WB-TLG were revealed to be independent prognostic factors regarding PFS and OS. However, in the central type, stage was the only independent prognostic factor in all of the models, and none of the PET/CT parameters were significant as shown in the forest plot analysis (Figure 2).

Subgroup analysis

The number of patients in the different subgroups is detailed in Table 4. The number of patients grouped by stage and WB-TLG matched exactly with that for stage and WB-MTV. Since MTV and TLG are interchangeable, the results are demonstrated together in the table. No significant bias was seen regarding the distribution of patient number in each subgroup. Kaplan–Meier curves were produced for each tumour location, divided into four groups involving stage and WB-MTV/TLG (Figure 4). No statistical difference was found concerning patient outcome between the central and peripheral types, both in terms of PFS ($p = 0.85$) and OS ($p = 0.73$) (Figure 3). In the peripheral type, patients with LD with low WB-MTV/TLG showed significantly better prognosis than all of the other groups, with the exception of patients with ED with low WB-MTV/TLG, after adjustment using the Bonferroni correction. If WB-MTV/TLG was high, the prognosis was very poor even in patients with LD and was equivalent to the prognosis for patients with ED (Figure 4c, d, g and h and Table 5). In the central type, patients with ED with low WB-MTV/TLG had a worse prognosis than was the case for patients with LD with high WB-MTV/TLG regarding OS (Figure 4b and f); this finding supported the results of the multivariate analysis.
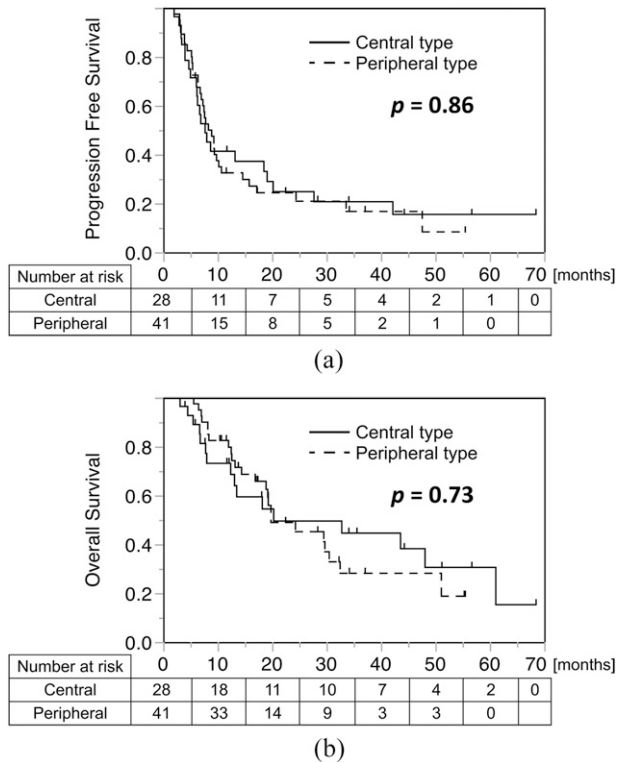
DISCUSSION

In the present study, we categorized patients with SCLC into two types based on tumour location, peripheral and central, and evaluated several parameters measured using pre-treatment FDG-PET/CT scans for the prediction of prognosis. Our results demonstrated that the independent prognostic factor was stage in the central type, but volumetric parameters such as WB-MTV/TLG in the peripheral type. Neither P-SUV$_{max}$ nor H-SUV$_{max}$ had much influence on prognosis in both types. Kaplan–Meier subgroup analysis was performed to support the multivariate analysis results. It showed that patients with peripheral type with LD and low WB-MTV/TLG had a better prognosis than those with the other groups, and patients with LD with high WB-MTV/TLG had a poor prognosis equivalent to patients with ED; this was not observed in the central type. When adjusted using Bonferroni correction, the p-value for the comparison between LD with low WB-MTV/TLG and ED with low WB-MTV/TLG in the peripheral type was not statistically significant; this is probably the result of the small number of patients evaluated and does not necessarily mean that stage is an

Table 4. Number of patients assigned to subgroups on the basis of stage and metabolic tumour volume (MTV) [total lesion glycolysis (TLG)]

Groups	Limited disease	Extensive disease	Total
Central type			
Low WB-MTV(TLG)	10	4	14
High WB-MTV(TLG)	4	10	14
Total	14	14	28
Peripheral type			
Low WB-MTV(TLG)	18	2	20
High WB-MTV(TLG)	6	15	21
Total	24	17	41

WB-MTV, whole-body metabolic tumour volume; WB-TLG, whole-body total lesion glycolysis.

Figure 3. Kaplan–Meier analyses of progression-free survival (a) and overall survival (b) according to tumour location. Patients who were censored are indicated as tick marks. No significant difference in prognosis was observed between patients with the central and peripheral types.

(a)

Number at risk	0	10	20	30	40	50	60	70 [months]
Central	28	11	7	5	4	2	1	0
Peripheral	41	15	8	5	2	1	0	

(b)

Number at risk	0	10	20	30	40	50	60	70 [months]
Central	28	18	11	10	7	4	2	0
Peripheral	41	33	14	9	3	3	0	

impractical prognostic factor in patients with peripheral type. To summarize, in the peripheral type, PET volumetric parameters could help in extracting patients with better prognosis, especially in patients with LD. However, in the central type, stage had more influence on prognosis than PET volumetric parameters. To our knowledge, the present study is the first to investigate the difference in prognostic power in terms of primary tumour location using FDG-PET/CT.

Subgroup analysis in relation to tumour location in SCLC has not been fully investigated. Only a few reports have discussed the relationship between tumour location regarding pre-treatment images and prognosis. Lally et al[14] reported that the location of the main bronchus was one of the mortality risks, together with older age, male sex and African-American ethnicity in multivariate analysis. Bandoh et al[13] reported that CEA levels in the peripheral type were significantly higher than those in the central type, but no significant difference in prognosis was found between the peripheral and central types. In surgical series, no significant prognostic difference has been reported between central-type and peripheral-type tumours,[16,17] which was also demonstrated in our study. Therefore, differences in prognosis according to tumour location remain controversial. However, as a new insight, we have revealed a possible prognostic difference in terms of glucose metabolic consumption, depending on whether the primary tumour was located in the centre or periphery of CT scans. One possible reason for this is that patients

with central type had a significantly larger WB-MTV/TLG than patients with peripheral type in our population. This means that patients with central type with a "low" WB-MTV/TLG had a tumour volume that was large enough to result in a poor clinical course. The central-type tumour is often very difficult to detect at an early stage and is found late when it is already large with lymph-node metastases. Then, WB-MTV/TLG would not contribute significantly to the prediction of the prognosis. The other reason is that there could be some biological differences between the peripheral and central types of SCLC. According to Nomori et al,[26] undifferentiated carcinoma of the small-cell type was located more frequently at the periphery of the lung than classical neuroendocrine types, such as oat-cell carcinoma and small-cell carcinoma of the intermediate cell type in surgical series. Most of the SCLC cases are diagnosed using a punch biopsy and are not often surgically resected; this makes it difficult to survey the entire range of tumour characteristics before treatment. There might also be a possible heterogeneity in SCLC, which is undetectable by mere biopsy. It would be meaningful to determine the difference in prognostic factors using non-invasive methods such as PET/CT according to subgroups (*e.g.* tumour location).

Several studies have demonstrated the prognostic value of FDG-PET parameters. However, the prognostic value of SUV_{max} is still controversial in SCLC. Pandit et al reported that a high SUV_{max} was significantly associated with poor survival,[27] while the difference in OS according to the SUV_{max} of the primary tumour was not found to be statistically significant in two independent studies.[28,29] SUV_{max} may have a complex relationship with prognosis in SCLC, unlike NSCLC, in which a favourable relationship with prognosis has already been reported in several studies.[29–33] This may reflect the characteristics of SUV_{max}, which shows the location where FDG uptake is highest within VOI. Conversely, FDG-PET volumetric parameters such as MTV and TLG are generally reported to be favourable prognostic factors. Furthermore, most of the previous studies have focused on WB-MTV in SCLC, unlike other malignancies, in which only the MTV of the primary tumour is usually investigated. For example, Zhu et al[12] reported WB-MTV as one of the important prognostic factors in patients with SCLC. Oh et al[10] reported that the sum of the extrathoracic MTVs is an independent prognostic biomarker for patients with ED with SCLC. Their results are reasonable, considering the biological nature of SCLC. Because the clinical course of SCLC is generally very rapid, the prognosis would correlate well with WB-MTV, which provides information concerning the total tumour burden and glucose metabolism in the entire target lesion. On the other hand, the MTV of the primary tumour would not directly reflect prognosis; the primary tumour in patients with SCLC can be very small, even if it is accompanied by severe lymphatic and metastatic spread. Overall, FDG-PET whole-body volumetric parameters can be said to be significant prognostic factors in SCLC. However, in our study, they were only found to be independent in the peripheral type, when focusing on the primary tumour location. Especially in the case of LD, patients with high WB-MTV/TLG had a poor prognosis similar to the patients with ED. This means that more careful observation for recurrence would be required, even if these patients once showed a good response to radical therapies.

Figure 4. Kaplan–Meier analyses of overall survival and progression-free survival subgrouped by stage and whole-body metabolic tumour volume (WB-MTV) (a, b, e and f) and whole-body total lesion glycolysis (WB-TLG) (c, d, g and h). In the peripheral type (a–d), patients with limited disease with low WB-MTV/TLG showed significantly better prognosis than the other groups, with the exception of extensive disease with low WB-MTV/TLG. In the central type (e–h), WB-MTV and WB-TLG did not contribute much to prognosis as compared with the peripheral type. ED, extensive disease; LD, limited disease; MTV, metabolic tumour volume; TLG, total lesion glycolysis. *, $p < 0.0083$ (adjusted by Bonferroni correction).
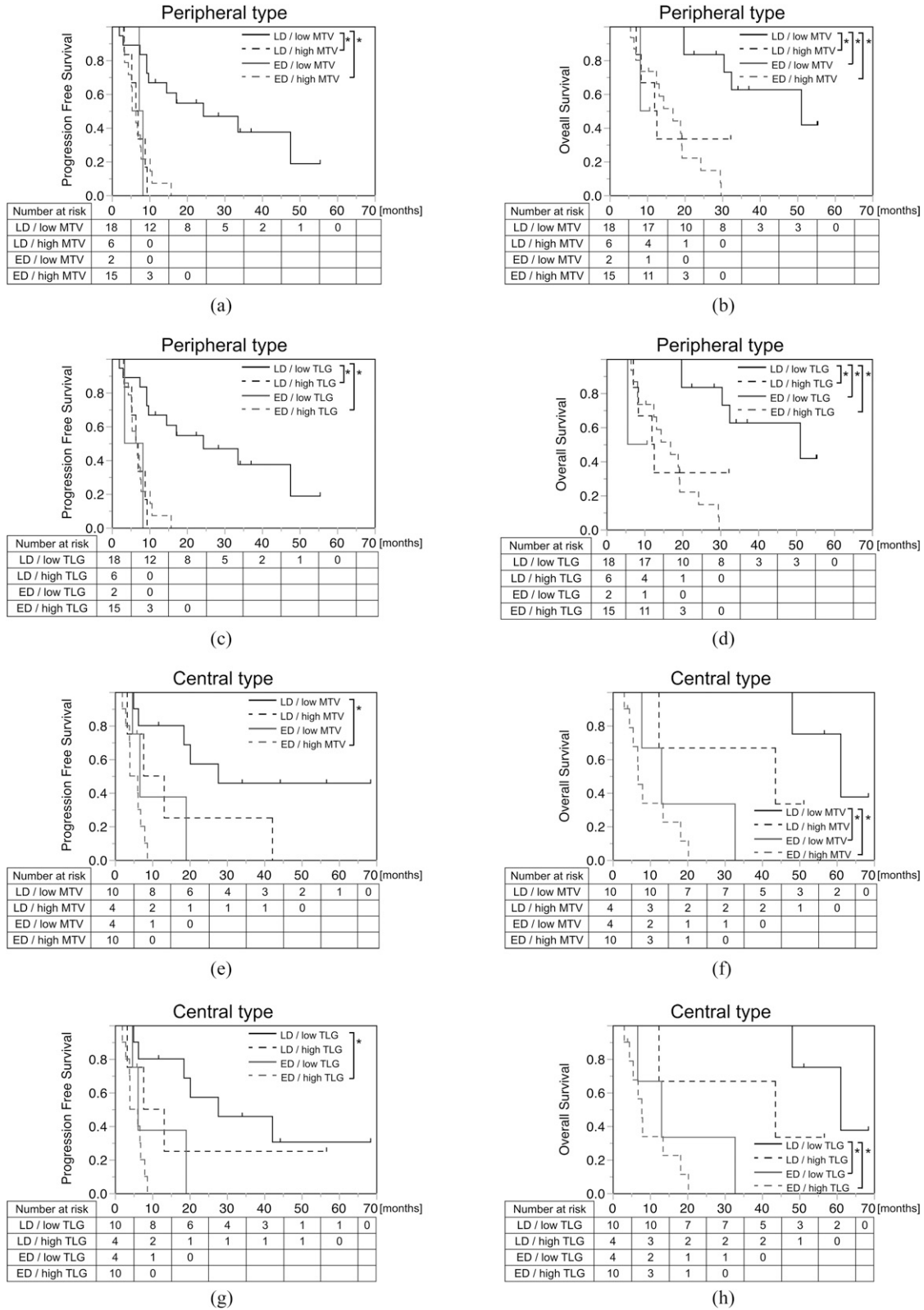
Table 5. *p*-values for Kaplan–Meier analysis according to each subtype using the log-rank test

Groups	Central		Peripheral	
	PFS	OS	PFS	OS
WB-MTV				
LD/low MTV *vs* LD/high MTV	0.093	0.10	0.0005[a]	0.0022[a]
LD/low MTV *vs* ED/low MTV	0.056	0.0003[a]	0.013	0.0036[a]
LD/low MTV *vs* ED/high MTV	0.0002[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]
LD/high MTV *vs* ED/low MTV	0.71	0.20	0.93	0.68
LD/high MTV *vs* ED/high MTV	0.078	0.030	0.82	0.54
ED/low MTV *vs* ED/high MTV	0.17	0.22	0.74	0.65
WB-TLG				
LD/low TLG *vs* LD/high TLG	0.39	0.098	0.0005[a]	0.0022[a]
LD/low TLG *vs* ED/low TLG	0.036	0.0003[a]	0.013	0.0036[a]
LD/low TLG *vs* ED/high TLG	0.0002[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]
LD/high TLG *vs* ED/low TLG	0.43	0.17	0.62	0.51
LD/high TLG *vs* ED/high TLG	0.078	0.033	0.70	0.56
ED/low TLG *vs* ED/high TLG	0.21	0.28	0.83	0.30

ED, extensive disease; LD, limited disease; MTV, metabolic tumour volume; OS, overall survival; PFS, progression-free survival; TLG, total lesion glycolysis; WB-MTV, whole-body metabolic tumour volume; WB-TLG, whole-body total lesion glycolysis.
[a]$p < 0.0083$ (adjusted using the Bonferroni correction).

In the present study using univariate analysis, NSE was one of the prognostic factors in patients with SCLC in both the central and peripheral types. The prognostic role for tumour markers in SCLC has not been fully established to date; however, some studies have investigated the relationship between prognosis and tumour markers.[34–36] Shibayama et al[36] reported on the complementary role of NSE and ProGRP; NSE was found to be superior to ProGRP as a prognostic factor, while ProGRP was more sensitive than NSE regarding the diagnosis of SCLC. Similar to the previous study, the pre-treatment serum NSE level showed a much better correlation with prognosis than ProGRP in our population; however, it was not found to be an independent prognostic factor, when adjusted for stage and PET volumetric parameters.

Our study had several limitations. First, it was non-randomized and retrospective in design and involved a small number of patients. Especially when divided into subgroups, the numbers of patients with ED with low MTV/TLG and patients with LD with high MTV/TLG were extremely small for analysis. Regimens equivalent to standard chemotherapy were used for the treatment of all of the patients; however, they were not unified. Some patients could not complete chemotherapy because of severe toxicity. These factors possibly confounded our study results, although no prominent bias was seen in our population. Second, brain metastasis, which is one of the major prognostic factors, was not considered in the evaluation of PET parameters because of high physiological FDG uptake in the normal tissue. In our population, approximately one-third of patients with ED had brain metastasis. A different prevalence rate between central type (25.0%) and peripheral type (7.3%) might have affected the

results. Third, because three different PET/CT scanners were used, absolute quantitative values might be unreliable. However, we confirmed the consistency of the cross-calibration factor with an error of <5% for each scanner, which would support the reproducibility of the data.[37] Moreover, the definition of tumour location used in the present study was based on the Timmerman criteria for NSCLC involving radiation therapy and has not been previously applied for SCLC. There have been no recent studies entailing precise evaluation of primary tumour location using CT; the tumour border was determined using chest X-rays.[13,14,26] Because no clear definition concerning central-type or peripheral-type tumours has been established, we applied the Timmerman criteria as a preliminary approach. Potentially, a more feasible border exists elsewhere in terms of biological features. To overcome these issues, further prospective studies involving more patients will be necessary to elucidate the prognostic value of volumetric PET/CT parameters.

CONCLUSION
The FDG-PET volumetric parameters were demonstrated to be significant and independent prognostic factors in the peripheral type of SCLC, whereas PET-based volumetric parameters were not shown to be independent prognostic factors in the central type. It may be necessary to take into account the location of the primary tumours, when considering the prognostic value of FDG-PET/CT in patients with SCLC.

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