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Usefulness of ^{18}F-α-Methyltyrosine PET for Therapeutic Monitoring of Patients with Advanced Lung Cancer

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Abstract. *Background/Aim: L-[3-^{18}F]-α-methyl tyrosine (^{18}F-FAMT) positron emission tomography (PET) has a high specificity for detecting malignant lesions. However, the usefulness of therapeutic monitoring of ^{18}F-FAMT PET against advanced human neoplasms remains unclear. Here, we evaluated ^{18}F-FAMT PET clinical significance regarding therapy response and outcome after systemic chemotherapy in patients with advanced lung cancer, compared to ^{18}F-FDG PET. Patients and Methods: All patients with untreated advanced lung cancer received ^{18}F-FAMT PET and ^{18}F-FDG PET before and 4 weeks after one cycle of chemotherapy. Metabolic response (MR) was defined according to the PERCIST guideline. Results: Ninety-five patients were eligible for analysis on both PET scans. The histological type included 87 non-small cell lung cancers and 8 small-cell lung cancers. Post-treatment maximal standardized uptake values (SUV_{max}) and MR on ^{18}F-FAMT PET were correlated with tumor response. In all patients, post-treatment SUV_{max} of ^{18}F-FDG and ^{18}F-FAMT PET and MR of ^{18}F-FAMT PET were statistically significant prognostic markers for predicting poor outcome by univariate analysis. Multivariate analysis confirmed that MR on ^{18}F-FAMT PET was a significant independent prognostic factor. Conclusion: MR on ^{18}F-FAMT PET may be a potential parameter to predict the prognosis after first-line chemotherapy in patients with advanced lung cancer.*

A significant clinical use of positron emission tomography (PET) in oncology is to evaluate by staging of various malignancies types (1, 2) Recently, many researchers have described usefulness of PET with 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) for monitoring the therapeutic effect of malignancy tumors. ^{18}F-FDG PET can detect metabolic alteration of cancer cells, thus, several studies have analyzed metabolic response (MR) by ^{18}F-FDG to predict the therapeutic efficacy and outcome of cancer patients (3-5). In addition, it has been reported that computed tomography (CT) perfusion is effective for monitoring therapeutic response after chemotherapy (6) and apparent diffusion coefficient by diffusion-weighted magnetic resonance imaging is associated with prognosis after surgery in human neoplasms (7). However, ^{18}F-FDG PET has limitation in tumor specificity since it can show false-positive results in benign diseases (8). The increased accumulation of ^{18}F-FDG partially depends on the presence of active inflammatory changes in the tumor tissue. There is no established clinical marker yet to predict the response and outcome of chemotherapy in cancer patients.

We have been examining the clinical significance of L-[3-^{18}F]-α-methyl tyrosine (^{18}F-FAMT) PET in various human cancers (9-12). ^{18}F-FAMT is accumulated in tumor specifically *via* the L-type amino acid transporter 1 (LAT1)

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protein, but not *via* LAT2 (9, 13). LAT1 is highly expressed in many types of neoplasms and plays critical roles in cellular growth and proliferation (14). Specificity of ^{18}F-FAMT has resulted in the usefulness for differentiating benign lesions from malignant tumors and predicting poor outcome in patients with lung cancer (8, 15). A preliminary study showed that ^{18}F-FAMT PET could be used for monitoring efficacy and predicting outcome of patients with lung cancer (16). However, that study included only 18 patients who underwent chemotherapy/chemoradiotherapy, therefore, further study was warranted to evaluate the clinical value of ^{18}F-FAMT PET to assess therapeutic response in lung cancer. Since ^{18}F-FAMT PET compared to ^{18}F-FDG PET is highly specific for malignant tumors (8, 9) we hypothesized that ^{18}F-FAMT might be more appropriate than ^{18}F-FDG for therapeutic monitoring after chemotherapy. The present study was performed to evaluate the potential usefulness of ^{18}F-FAMT PET in monitoring therapeutic response and survival in patients with advanced lung cancer.

Patients and Methods

Patients. The study was prospectively conducted on patients with advanced lung cancer at Gunma University Hospital, Japan. The inclusion criteria consisted of the following: 1. Pathologically-proven lung cancer; 2. Inoperable stage III or stage IV candidate for chemotherapy as an initial treatment, as defined by the American Joint Committee on Cancer staging system (AJCC) and the Union Internationale Centre le Cancer (15); 3. Eastern Cooperative Oncology Group (ECOG) performance status 0-2; 4. ^{18}F-FAMT PET/CT and ^{18}F-FDG PET/CT scheduled before and after the first cycle of initial chemotherapy; 5. No evidence of concurrent cancer; 6. No uncontrolled diabetes. Pre-treatment PET/CT studies were performed as part of the staging work-up before the initial chemotherapy. The patients also underwent chest CT, whole-body bone scan and bronchoscopy. Post-treatment PET/CT scans were required at approximately 4 weeks after the first cycle of chemotherapy. The protocol required that both pre- and post-treatment PET scans had to be performed on the same scanner. The study was approved by the institutional review board (Gunma University 821) and was conducted in accordance with the declaration of Helsinki and Good Clinical Practice guidelines. The patients were required to provide informed consent.

One hundred eleven consecutive patients were enrolled in this study between October 2008 and February 2013. Of these patients, 16 were ineligible for this study, because twelve patients did not have evaluable post-treatment PET and 4 were not treated with chemotherapy as an initial treatment. Thus, a total of 95 patients were eligible for this study.

The patient's demographics are listed in Table I. Their median age was 69 years, ranging from 32 to 85 years. Fifty-six percent of all patients had performance status (PS) of 0, 43% had PS of 1, and a patient had PS of 2. The majority of patients had a non-small-cell lung cancer (NSCLC) histology (92%, n=87) and only 8 patients (8%) had a histology of small-cell lung cancer (SCLC). As a first-line treatment, 70 patients received systemic chemotherapy and 25 patients were treated with concurrent thoracic chemo-radiotherapy (CRT) because of locally advanced lung cancer. Out of 8 patients with SCLC, 2 received concurrent thoracic CRT including cisplatin plus etoposide and the others were treated with chemotherapy including cisplatin plus etoposide in 4 patients and carboplatin plus etoposide in 2 patients. Out of 87 patients with NSCLC, 59 patients received chemotherapy including platinum-based regimens, platinum-based regimens with bevacizumab in 21 patients and non-platinum-based regimens in 7 patients, and 23 patients were treated with concurrent thoracic CRT including cisplatin plus S-1 in 18 patients and carboplatin plus paclitaxel in 5 patients. Sixty-five patients received second line chemotherapy after initial chemotherapy. As second or third line chemotherapy, 15 patients received epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI).

Table I. *Patients' characteristics*.

Characteristics	Number (n=95)	Percentage (%)
Age, years		
Median	69	
Range	32-85	
Gender		
Male	71	75
Female	24	25
ECOG performance status		
0	53	56
1	41	43
2	1	1
Histology		
Adenocarcinoma	55	58
Squamous cell carcinoma	21	22
Large cell carcinoma	5	5
Small cell carcinoma	8	8
Other	6	7
Clinical stage		
IIIA	18	19
IIIB	23	24
IV	54	57
Chemotherapy regimen		
Platinum-based combination	67	71
Platinum-based regimen with bevacizumab	21	22
Non-platinum regimen	7	7
Concurrent thoracic chemo-radiotherapy		
Yes	25	26
No	70	74
Response to first-line chemotherapy		
CR+PR	46	48
SD+PD	49	52

ECOG, European Clinical Oncology Group; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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

PET imaging and data analysis. ^{18}F-FAMT was synthesized in our cyclotron facility using a method described previously (18). In brief,

^{18}F-FAMT was synthesized *via* direct electrophilic substitution of α-methyl-L-tyrosine with [^{18}F]F_2 gas. The radiochemical yield of ^{18}F-FAMT was approximately 20%, and its radiochemical purity was approximately 99%. ^{18}F-FDG was also produced in our facility as described previously (9). In brief, ^{18}F-FDG was synthesized *via* nucleophilic substitution of mannose triflate with fluoride [^{18}F]F^-. The patients fasted for at least 6 h before PET imaging. PET imaging was performed using a PET/CT scanner (Discovery STE, GE Healthcare, Waukesha, WI, USA) with a 700 mm field of view. Three-dimensional data acquisition was initiated 50 minutes after injection of 5 MBq/kg of ^{18}F-FAMT or 5 MBq/kg of ^{18}F-FDG. We acquired 4 to 10 bed positions (3-minute acquisition per bed position) according to the range of the imaging. Attenuation-corrected transverse images obtained with ^{18}F-FAMT and ^{18}F-FDG were reconstructed with the ordered-subsets expectation maximization algorithm into 128×128 matrices with a slice thickness of 3.27 mm.

All ^{18}F-FDG and ^{18}F-FAMT PET images were interpreted by two experienced nuclear physicians. The interpreting physicians were unaware of the patient's clinical history and data. Tracer uptake in the primary tumor was defined as positive if the uptake was higher than the uptake in the normal mediastinum. Discrepant results were resolved by consensus review. For the semi-quantitative analysis, functional images of the standardized uptake value (SUV) were generated based on the attenuation-corrected transaxial images, the injected doses of ^{18}F-FAMT and ^{18}F-FDG, the patient's body weight, and the cross-calibration factor between PET and the dose calibrator. SUV was defined as radioactive concentration in the region of interest (ROI) [MBq/g] divided by injected dose (MBq) and patient's body weight (g) [SUV=ROI/(MBq/g)].

The ROI was manually drawn over the primary tumor on the SUV images. When the tumor was larger than 1 cm in diameter or the shape of the tumor was irregular or multifocal, a ROI of approximately 1 cm in diameter was drawn over the area corresponding to the maximal tracer uptake. ROI analysis was conducted by a nuclear physician with the aid of corresponding CT scans. The maximal SUV (SUV_{max}) in the ROI was used as a representative value for the assessment of ^{18}F-FAMT and 18F-FDG uptake in the lesion. CT scan for the purpose of initial staging was done with intravenous contrast medium. CT images were interpreted by the board-certified radiologists.

Response assessment and statistical analysis. Tumor response was assessed on both CT scans and PET. CT-based tumor response was evaluated according to Response evaluation criteria in solid tumor (RECIST) and used as a reference standard (19). PET-based MR was defined as a reduction in ^{18}F-FDG or ^{18}F-FAMT uptake of 30% or greater according to the PERCIST guideline (4).

Progression-free survival (PFS) was defined as the time from initial chemotherapy to disease progression or death. Overall survival (OS) was determined as the time from initial chemotherapy to death from any cause. Survival estimation was performed using the Kaplan-Meier method and the log-rank test. *p*-Values <0.05 were used to indicate a statistically significant difference. Fisher's exact test was used to examine the association between two categorical variables. The correlation between different variables was analyzed using the Pearson's rank test. Multivariate analyses were performed using a stepwise Cox proportional hazards model to identify independent prognostic factors. Statistical analyses were performed using JMP 8 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Response assessment and PET imaging. Out of 95 assessable patients, 46 responded to initial chemotherapy with an overall response rate of 48%. Two patients achieved complete response (CR) and 44 partial response (PR), whereas 34 patients had stable disease (SD) and 15 progressive disease (PD).

The primary tumors of 95 patients were analyzed with regard to pre-treatment SUV_{max}, post-treatment SUV_{max} and MR in both ^{18}F-FDG PET and ^{18}F-FAMT PET. The median pre-treatment SUV_{max} and post-treatment SUV_{max} of ^{18}F-FAMT were 2.0 (range 0.5 to 8.0) and 1.4 (range 0.4 to 4.8), respectively ($p<0.001$), and those of ^{18}F-FDG were 9.8 (range 1.6 to 29.6) and 5.7 (range 0.8 to 20.5), respectively ($p<0.001$). Statistically significant correlation was observed between ^{18}F-FDG and ^{18}F-FAMT PET at both pre and post-treatment SUV_{max}. The cut-off values to discriminate high and low SUV_{max} groups were defined according to the median pre-treatment SUV_{max} values in both PET studies and were analyzed using the patient's clinical characteristics (Table II). High pre-treatment SUV_{max} of ^{18}F-FAMT was significantly correlated with male sex ($p<0.001$), pre-treatment SUV_{max} ($p=0.004$) and post-treatment SUV_{max} ($p=0.026$) of ^{18}F-FDG. High post-treatment SUV_{max} of ^{18}F-FAMT yielded a significant correlation with age ($p=0.006$), histology type ($p=0.004$), response according to RECIST ($p<0.001$) and pre-treatment SUV_{max} ($p<0.001$) and post-treatment SUV_{max} ($p<0.001$)of ^{18}F-FDG. Images of PET studies in a patient were shown in Figure 1A and B.

MRs on ^{18}F-FAMT PET and ^{18}F-FDG PET were observed in 38.9% and 57.8% of patients, respectively ($p<0.001$). MR on ^{18}F-FAMT PET had a statistically significant association with response according to RECIST, post-treatment SUV_{max} of ^{18}F-FDG and MR on ^{18}F-FDG PET ($p<0.001$). Moreover, post-treatment SUV_{max} of ^{18}F-FAMT PET was significantly lower in CR and PR patient group compared to the SD ($p=0.042$) and PD ($p=0.010$) groups, but no statistically significant different between SD and PD groups ($p=0.354$) (Figure 2A). A statistically significant difference in post-treatment SUV_{max} between responders (CR and PR) and non-responders (SD or PD) and no significant difference between SD and PD was observed also for ^{18}F-FDG PET (Figure 2B).

Survival analysis. The median PFS and OS for all patients were 268 days and 499 days, respectively. Median follow-up period was 304 days, ranging from 103 days to 1658 days. Sixty-nine patients had a recurrence after initial treatment and 51 patients died due to progressive disease of lung cancer. The survival analysis of prognostic factors is presented in Table III and the Kaplan-Meier curves

Table II. *Patients' characteristics according to ^{18}F-FAMT uptake.*

Characteristics	Pre-treatment SUV_{max}			Post-treatment SUV_{max}			Metabolic response		
	High (n=45)	Low (n=50)	*p*-Value	High (n=25)	Low (n=70)	*p*-Value	Yes (n=37)	No (n=58)	*p*-Value
Age									
≤65 yr	12	21	0.135	3	30	0.006	15	18	0.382
>65 yr	33	29		22	40		22	40	
Gender									
Male	36	35	<0.001	20	51	0.596	27	44	0.812
Female	9	15		5	19		10	14	
ECOG performance status									
0	24	29	0.683	12	41	0.482	22	31	0.672
1 and 2	21	21		13	29		15	27	
Histology									
Adenocarcinoma	16	39	0.205	8	47	0.004	20	35	0.670
Non-adenocarcinoma	29	11		17	23		17	23	
Clinical stage									
III	13	12	0.645	5	20	0.597	10	15	>0.999
IV	32	38		20	50		27	43	
Response to first-line chemotherapy									
CR+PR	22	24	>0.999	8	38	<0.001	25	21	0.003
SD+PD	23	26		17	32		12	37	
Pre-treatment SUV_{max} of ^{18}F-FDG									
High	29	17	0.004	20	26	<0.001	18	28	>0.999
Low	16	33		5	44		19	30	
Post-treatment SUV_{max} of ^{18}F-FDG									
High	19	10	0.026	17	12	<0.001	7	22	0.068
Low	26	40		8	58		30	36	
Metabolic response on ^{18}F-FDG									
Yes	23	32	0.219	11	44	0.156	26	29	0.058
No	22	18		14	26		11	29	

ECOG, european clinical oncology group; MR, metabolic response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SUV_{max}, maximal standardized uptake value.

according to the results of both PET studies are shown in Figure 3. Univariate analysis for OS demonstrated that PS, post-treatment SUV_{max} of ^{18}F-FAMT and ^{18}F-FDG and MR on ^{18}F-FAMT PET were significant predictors of a poor prognosis. Multivariate analysis confirmed that PS, post-treatment SUV_{max} of ^{18}F-FDG and MR on ^{18}F-FAMT PET were independent and significant predictors of poor prognosis. The analysis for PFS showed that PS and post-treatment SUV_{max} of ^{18}F-FAMT and ^{18}F-FDG were significantly associated with poor prognosis and PS and post-treatment SUV_{max} of ^{18}F-FDG were confirmed as an independent prognostic factors by multivariate analysis.

Next, we performed univariate and multivariate analyses of OS and PFS on 70 patients who received only chemotherapy (Table IV). PFS analysis revealed that age, PS, histology, and post-treatment SUV_{max} of ^{18}F-FAMT and ^{18}F-FDG were significant factors for predicting poor outcome, however, only PS was confirmed as an independent predictor by multivariate analysis.

Discussion

The present study prospectively investigated the clinical significance of ^{18}F-FAMT PET as a means of therapeutic monitoring in patients with advanced lung cancer. This study directly compared ^{18}F-FAMT PET with ^{18}F-FDG PET and revealed that changes in the amino-acid tracer uptake defined by MR on ^{18}F-FAMT PET could be an independent and significant prognostic factor for predicting poor outcome after chemotherapy. Post-treatment SUV_{max} of ^{18}F-FAMT PET and ^{18}F-FDG PET were both significantly associated with short survival time after initial chemotherapy and that of ^{18}F-FDG PET was identified as an independent predictor by multivariate analysis. MR on ^{18}F-FDG PET could not predict therapeutic response and outcome after chemotherapy. These results indicate that post-treatment SUV_{max} on ^{18}F-FDG PET and MR on ^{18}F-FAMT PET are clinically significant as predictors for survival after initial chemotherapy in patients with advanced lung cancer.

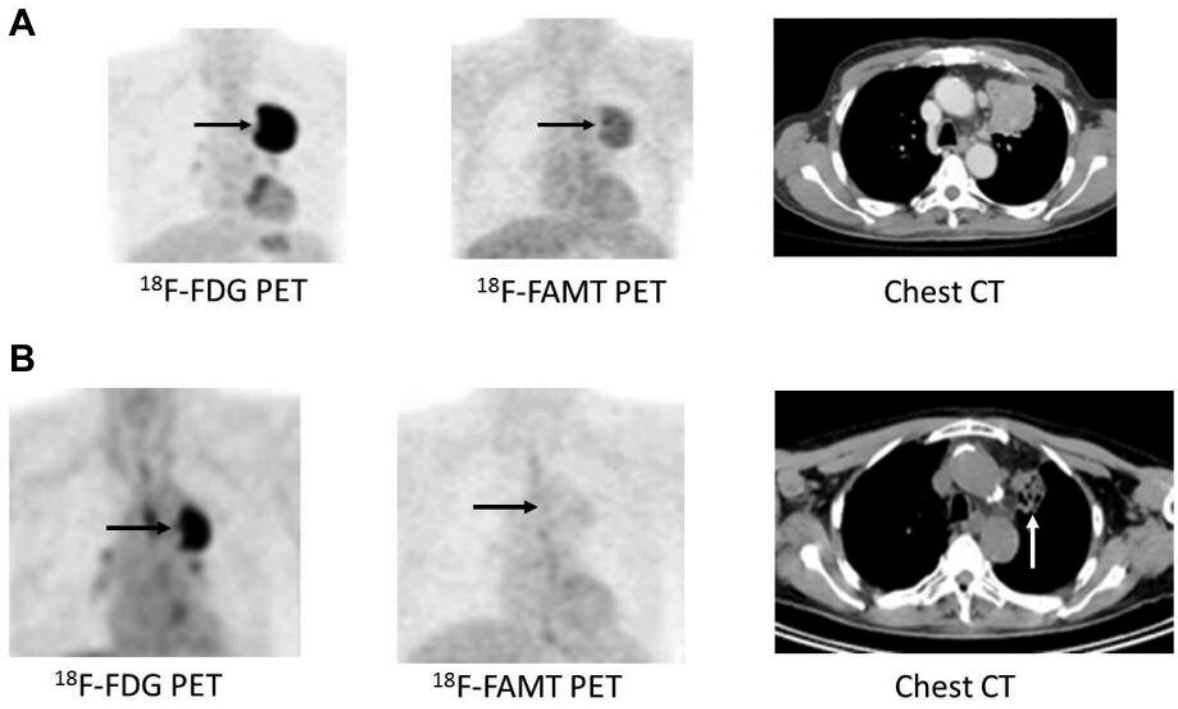

Figure 1. *Images of ^{18}F-FDG PET, ^{18}F-FAMT PET and chest CT at baseline and after 1 cycle of chemotherapy in a 72-year-old male with squamous cell carcinoma of left lung (cT2N2M1, c-stage IV) (A) Coronal view of ^{18}F-FDG PET and ^{18}F-FAMT PET at baseline shows abnormal accumulation in the primary tumor (black arrows). Chest CT shows the primary tumor corresponding to the abnormal uptake on both PET studies (white arrow) (B) ^{18}F-FDG PET and ^{18}F-FAMT PET after one cycle of chemotherapy shows markedly decreased accumulation in the primary tumor (black arrows) and chest CT also shows reduction of primary tumor (white arrow).*

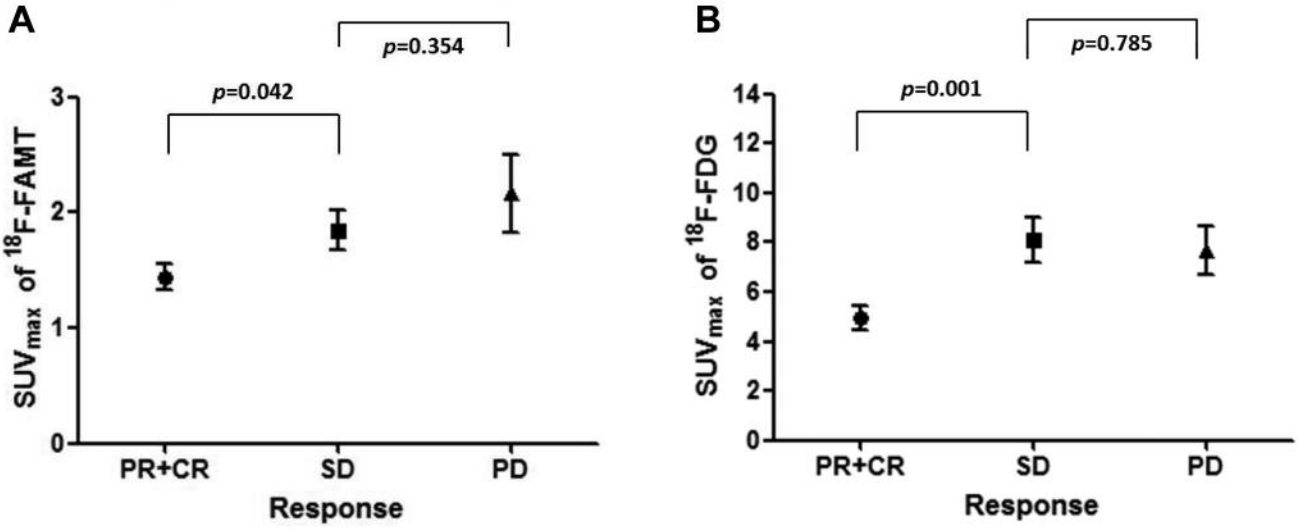

Figure 2. *Relationship between post-treatment SUV_{max} of PET and response by RECIST. (A) Post-treatment SUV_{max} of ^{18}F-FAMT PET was significantly lower in CR and PR than that in SD (p=0.042) or PD (p=0.010), but no statistically significant difference was observed between SD and PD (p=0.354). (B) Post-treatment SUV_{max} of ^{18}F-FDG PET was significantly lower in complete response (CR) and partial response (PR) than that in stable disease (SD) (p=0.001) or PD (p=0.008), but no statistically significant difference was observed between SD and PD (p=0.785).*

Table III. *Univariate and multivariate analysis in overall survival and progression-free survival in all patients (n=95).*

Variable	Overall survival					Progression-free survival				
	MST (days)	*p*-Value (univariate)	*p*-Value (multivariate)	Hazard Ratio	95% CI	MST (days)	*p*-Value (univariate)	*p*-Value (multivariate)	Hazard Ratio	95% CI
Age										
≤65 yr	496	0.195				304	0.184			
>65 yr	494					228				
Gender										
Male	496	0.877				296	0.839			
Female	483					247				
PS										
0	534	<0.001	<0.001	3.534	1.941	336	<0.001	<0.001	2.545	1.560
1 and 2	273				to 6.548	171				to 4.163
Clinical stage										
III	509	0.301	0.314	0.496	0.112	336	0.196	0.266	1.904	0.622
IV	424				to 1.887	226				to 6.478
Histology										
AC	508	0.212	0.455	0.797	0.444	304	0.061	0.126	1.493	0.891
Non-AC	453				to 1.453	181				to 2.482
Pre-treatment SUV_{max} of ^{18}F-FDG										
High	398	0.170				213	0.349			
Low	505					304				
Pre-treatment SUV_{max} of ^{18}F-FAMT										
High	516	0.673				210	0.637			
Low	489					304				
Post-treatment SUV_{max} of ^{18}F-FDG										
High	288	0.002	0.034	2.093	1.059	165	0.001	0.021	2.005	1.111
Low	523				to 4.079	319				to 6.478
Post-treatment SUV_{max} of ^{18}F-FAMT										
High	238	0.027	0.750	1.125	0.538	177	0.038	0.717	1.122	0.594
Low	516				to 2.315	311				to 2.079
Metabolic response on ^{18}F-FDG										
Yes	489	0.369				257	0.489			
No	502					258				
Metabolic response on ^{18}F-FAMT										
Yes	808	0.031	0.031	2.034	1.065	213	0.465			
No	426				to 4.157	286				

95% CI, 95% Confidence interval; MST, median survival time; PS, performance status; AC, adenocarcinoma; Non-AC, non-adenocarcinoma; SUV_{max}, maximal standardized uptake value.

The role of ^{18}F-FDG PET in the response assessment has been discussed in patients with advanced lung cancer (20-22). These studies have documented that a reduction of glucose metabolism after 1 or 2 cycles of chemotherapy is highly predictive for prognosis in patients (20-22). Weber *et al*. reported that a ≥20% decrease in SUV after 1 cycle of chemotherapy correlated with longer survival time (22), whereas, de Geus-Oei *et al*. described that a reduction in SUV of 35% or more after 2 or 3 cycles of chemotherapy was significantly predictive for outcome (21). The definition of MR after chemotherapy was slightly different in all the above studies. Lack of standardization and reproducibility regarding the measurement of therapeutic response may impair the role of ^{18}F-FDG PET as a prognostic marker. Moreover, the previous studies had limitation to analyze the prognostic significance due to a small sample size of 60 patients or less. In the present study, glucose MR according to PERCIST could not be predictive for prognosis after chemotherapy, but post-treatment SUV_{max} of ^{18}F-FDG PET was identified as a significant prognostic predictor. Recently, Machtay *et al*. described that higher post-treatment SUV_{max} of 18F-FDG PET is significantly associated with worse outcome for patients with stage III NSCLC who received concurrent platinum-based CRT (5). The study was the largest prospective study with assessable 173 patients and post-treatment ^{18}F-FDG PET was done at approximately 14 weeks after initial CRT (12 to 16 weeks). They concluded that it remains unclear about an optimal cut-off value as a prognostic factor, although

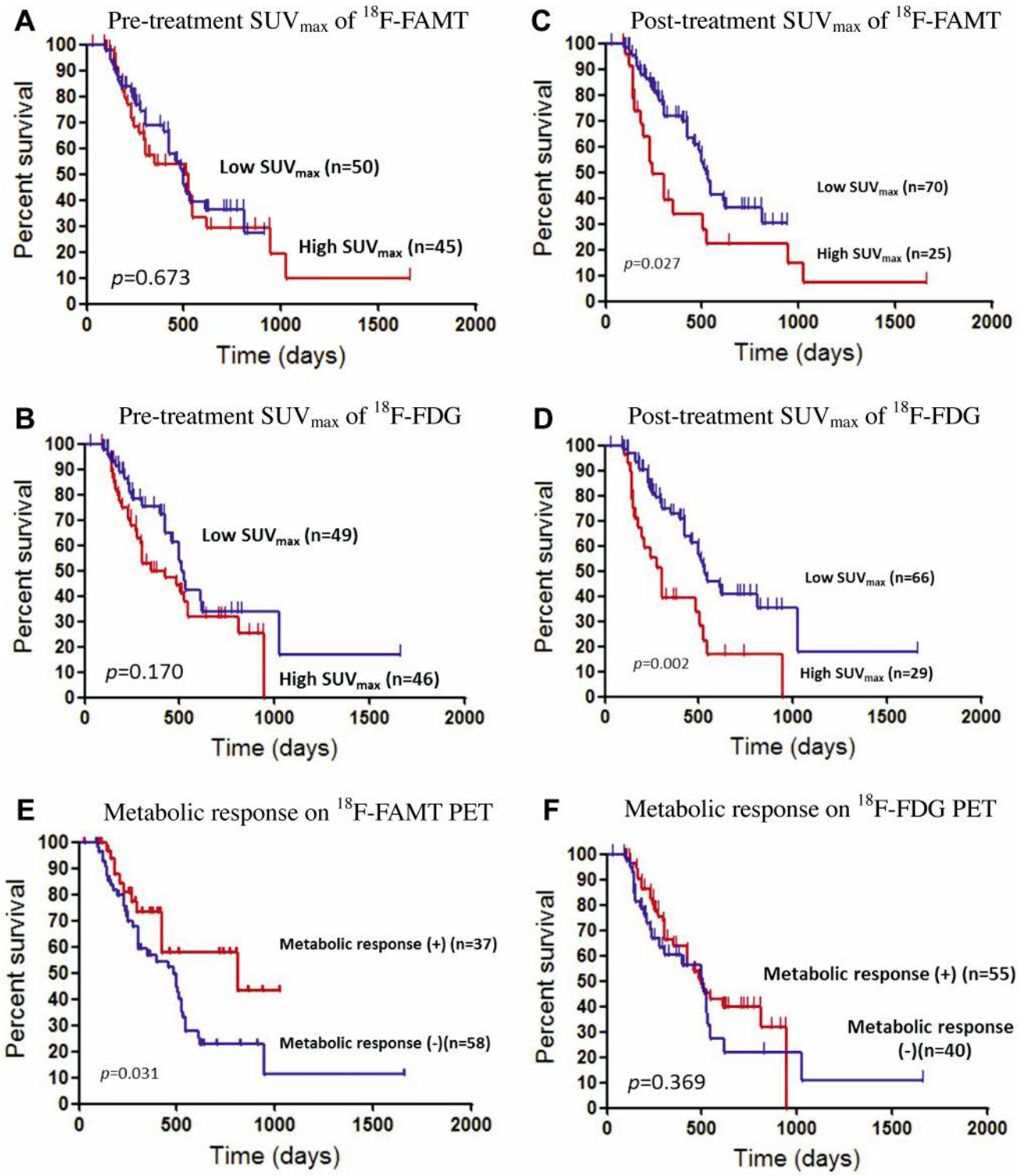

Figure 3. *Overall survival curve according to pre-treatment SUV_{max}, post-treatment SUV_{max} and metabolic response (MR) on both ^{18}F-FDG and ^{18}F-FAMT PET studies. Pre-treatment SUV_{max} of (A) ^{18}F-FAMT and (B) ^{18}F-FDG demonstrates no significant prognostic difference between patients with high and low uptake of the tumors. However, post-treatment SUV_{max} of both (C) ^{18}F-FAMT and (D) ^{18}F-FDG shows significant difference between patients with high and low uptake of the tumors (E) MR on ^{18}F-FAMT PET is a significant prognostic predictor but (F) MR on ^{18}F-FDG PET is not.*

Table IV. *Univariate and multivariate analysis in overall survival and progression-free survival in 70 patients who received chemotherapy only.*

Variable	Overall Survival					Progression-free survival				
	MST (days)	*p*-Value (univariate)	*p*-Value (multivariate)	Hazard Ratio	95% CI	MST (days)	*p*-Value (univariate)	*p*-Value (multivariate)	Hazard Ratio	95% CI
Age										
≤65 yr	520	0.051				311	0.017	0.405	1.321	0.689
>65 yr	303					198				to 2.610
Gender										
Male	305	0.765				213	0.897			
Female	483					226				
PS										
0	579	<0.001	<0.001	3.759	1.889	352	<0.001	<0.001	3.192	1.771
1	263				to 7.791	165				to 5.868
Histology										
AC	508	0.127	0.569	1.224	0.603	267	0.042	0.107	1.704	0.889
Non-AC	278				to 2.428	165				to 3.229
Pre-treatment SUV_{max} of ^{18}F-FDG										
High	303	0.052				206	0.161			
Low	519					238				
Pre-treatment SUV_{max} of ^{18}F-FAMT										
High	453	0.726				195	0.514			
Low	422					257				
Post-treatment SUV_{max} of ^{18}F-FDG										
High	277	<0.001	0.036	2.254	1.056	165	0.002	0.164	1.626	0.817
Low	534				to 4.645	257				to 3.194
Post-treatment SUV_{max} of ^{18}F-FAMT										
High	229	0.015	0.611	1.227	0.550	163	0.045	0.927	1.034	0.497
Low	520				to 2.679	293				to 2.085
Metabolic response on ^{18}F-FDG										
Yes	422	0.780				213	0.977			
No	459					226				
Metabolic response on ^{18}F-FAMT										
Yes	808	0.010	0.040	2.099	1.032	210	0.261			
No	302				to 4.634	236				

95% CI, 95% Confidence interval; MST, median survival time; PS, performance status; AC, adenocarcinoma; Non-AC, non-adenocarcinoma; SUV_{max}, maximal standardized uptake value.

a later reduction in tumor ^{18}F-FDG uptake was useful as a prognostic predictor following CRT. Although our study indicates that an early decrease in ^{18}F-FDG uptake after one cycle of chemotherapy is significantly predictive for survival after chemotherapy, there are no conclusive data to confirm the prognostic significance of ^{18}F-FDG PET in therapeutic response and survival, thus, further analysis is needed.

Amino acid PET tracers have been developed to overcome the limitation of false positive findings on ^{18}F-FDG PET (8, 9, 23, 24). To our knowledge, however, there is no established PET using available amino acid tracer as a predictor of therapeutic monitoring after systemic chemotherapy. The present study is a large prospective exploration investigating the usefulness of ^{18}F-FAMT PET as a therapeutic monitoring in advanced lung cancer. The results indicated that the uptake of ^{18}F-FAMT at baseline and after one cycle of chemotherapy were correlated with that of ^{18}F-FDG, while MR and post-treatment SUV_{max} on ^{18}F-FAMT PET were significantly associated with the response as evaluated by RECIST. A significant difference in the uptake of ^{18}F-FAMT was observed between responders and non-responders. MR on ^{18}F-FAMT PET was an independent prognostic factor after one cycle of the first-line chemotherapy in patients with advanced lung cancer. All patients including those who received concurrent CRT also showed same results. These findings suggest that the change in the amino acid metabolism plays a crucial role in the therapeutic efficacy and prognosis in advanced lung cancer. ^{18}F-FAMT has a fundamental drawback as a PET tracer as its tumor uptake is lower compared to ^{18}F-FDG. However, ^{18}F-FAMT is highly specific to malignant lesions without false-positive findings due to transport by the tumor-specific LAT1 (8, 9). Other amino acid PET tracers are

transported *via* other transporters expressing on non-malignant tumor cells. Previous study revealed that specificity of ^{18}F-FAMT to LAT1 is responsible to α-methyl moiety of the structural formula (13). As far as we have examined, ^{18}F-FAMT has been the most specific and avid to LAT1 among amino acid derivatives (data not shown). Therefore, we believe ^{18}F-FAMT is at present the amino acid PET tracer of choice for the assessment of therapeutic monitoring. We speculate that ^{18}F-FAMT would directly correspond to the tumor metabolic changes after chemotherapy and reflect growth or shrinkage of the tumor as compared to ^{18}F-FDG.

There are several limitations in the present study. Firstly, our enrolled population was not simply stratified because we included patients that underwent concurrent CRT, although the majority of patients (74%; 70/95) was stage IIIB or IV without medical suitability for concurrent CRT. Secondly, chemotherapy regimens were not unique. It may bias the results of the present study. Finally, cut-off value of SUV_{max} and definition of MR in this study were referred by the previous studies. Therefore, these definitions remain to be optimized by further studies. It is also mentioned that the metabolic parameters such as metabolic tumor volume or total lesion glycolysis may be accounted for a comparison (3). We should take them into account to verify the role of ^{18}F-FAMT PET if ^{18}F-FAMT PET is useful for therapeutic monitoring. In our study, moreover, the histological type of the tumors is different and different therapy regimens were applied for patients with the heterogeneity of histological types. This may bias the results of our study.

In conclusion, MR on ^{18}F-FAMT PET was identified as an independent factor to predict the prognosis after first-line chemotherapy in patients with advanced lung cancer. The value of post-treatment SUV_{max} on both ^{18}F-FDG and ^{18}F-FAMT PET could be a promising prognostic predictor. Further investigation in a large-scale study is warranted to verify the present results.

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