

Prognostic value of ^{18}F -fluoroazomycin arabinoside PET/CT in patients with advanced non-small-cell lung cancer

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Key words

^{18}F -fluoroazomycin arabinoside (FAZA), ^{18}F -fluorodeoxyglucose (FDG), non-small-cell lung cancer, positron emission tomography/computed tomography (PET/CT), prognosis

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This study evaluated the prognostic value of positron emission tomography/computed tomography (PET/CT) using ^{18}F -fluoroazomycin arabinoside (FAZA) in patients with advanced non-small-cell lung cancer (NSCLC) compared with ^{18}F -fluorodeoxyglucose (FDG). Thirty-eight patients with advanced NSCLC (stage III, 23 patients; stage IV, 15 patients) underwent FAZA and FDG PET/CT before treatment. The PET parameters (tumor-to-muscle ratio [T/M] at 1 and 2 h for FAZA, maximum standardized uptake value for FDG) in the primary lesion and lymph node (LN) metastasis and clinical parameters were compared concerning their effects on progression-free survival (PFS) and overall survival (OS). In our univariate analysis of all patients, clinical stage and FAZA T/M in LNs at 1 and 2 h were predictive of PFS ($P = 0.021$, 0.028 , and 0.002 , respectively). Multivariate analysis also indicated that clinical stage and FAZA T/M in LNs at 1 and 2 h were independent predictors of PFS. Subgroup analysis of chemoradiotherapy-treated stage III patients revealed that only FAZA T/M in LNs at 2 h was predictive of PFS ($P = 0.025$). The FDG PET/CT parameters were not predictive of PFS. No parameter was a significant predictor of OS. In patients with advanced NSCLC, FAZA uptake in LNs, but not in primary lesions, was predictive of treatment outcome. These results suggest the importance of characterization of LN metastases in advanced NSCLC patients.

Hypoxia results when oxygen supply fails to meet the demand of living tissue. Since the first demonstration of tumor hypoxia by Tomlinson and Gray,⁽¹⁾ many solid tumors, especially locally advanced tumors, have been shown to have areas of hypoxia.⁽²⁾ The presence of tumor hypoxia is recognized as a major cause of resistance to anticancer therapy.⁽³⁾ Furthermore, it has been clarified that, during the processes by which cancer cells adapt to hypoxic conditions, their malignant potential, including invasiveness and metastatic potential, increases through the upregulation of many proteins mediated by the activation of hypoxia inducible factor-1.^(4,5) Information on hypoxia is therefore important for the management of individual patients with cancer,⁽⁶⁾ and this information can be used for several purposes, including the selection of appropriate treatment strategies, as a prognostic indicator, and in radiation treatment planning.^(5,7)

Many PET probes targeting hypoxic microenvironments have been developed and tested in preclinical and clinical settings, including nitroimidazole compounds and $^{60,61,62,64}\text{Cu}$ -diacetyl-bis(N4-methylthiosemicarbazone).^(2,5,8) Among them,

^{18}F -fluoromisonidazole (FMISO) has been most widely applied for cancer patients,⁽⁹⁾ and its clinical value, including the correlation between tumor oxygen concentrations and tumor FMISO uptake and the relationship between FMISO tumor uptake and prognosis, has been documented.^(10,11) However, the specific uptake of FMISO by hypoxic tumors and its clearance from normoxic tissue are slow, resulting in a long uptake period (~4 h) and insufficient image contrast.⁽⁸⁾ ^{18}F -fluoroazomycin arabinoside (FAZA) is a second-generation nitroimidazole compound developed to overcome the limitations of FMISO.⁽¹²⁾ An animal study illustrated that FAZA displayed higher tumor-to-background ratios than FMISO, indicating the superior kinetics of FAZA.⁽¹³⁾ Clinical evaluation of FAZA is currently ongoing, and early results have been reported for head and neck, lung, prostate, and rectal cancers.^(14–17) However, the prognostic value of FAZA tumor uptake in clinical patients has not been fully evaluated. In the present study, we evaluated the prognostic value of FAZA PET/CT for patients with advanced non-small-cell lung cancer (NSCLC) in comparison to ^{18}F -fluorodeoxyglucose (FDG).

Patients and Methods

Patients. From February 2010 to February 2014, 42 consecutive patients suspected of having locally advanced NSCLC were prospectively enrolled in this study. Patients underwent PET/CT with FAZA and FDG along with conventional imaging workup for staging. After treatment, the clinical status of the patients, including the development of recurrence/metastasis and survival, was followed up. Histopathological examination or clinical follow-up including serial changes in imaging findings was used as a standard of reference. The study protocol was approved by the institutional review board. The study was carried out in accordance with the ethical standards of the Declaration of Helsinki of 1964 and all subsequent revisions. All patients provided written informed consent for participation in the study.

¹⁸F-fluoroazomycin arabinoside and FDG PET/CT. ¹⁸F-fluoroazomycin arabinoside was synthesized by direct fluorination of the tosyl precursor (5 mg; ABX, Radeberg, Germany) with ¹⁸F-F⁻, followed by hydrolysis with aqueous 0.1 M NaOH in the cyclotron facility of our institution.⁽¹⁸⁾ The specific radioactivity was >90 GBq/μmol (mean ± SD, 374 ± 218), and the radiochemical purity was >96% (mean ± SD, 99.4 ± 0.9). ¹⁸F-fluorodeoxyglucose was purchased from Nihon Medi-Physics (Tokyo, Japan).

The PET/CT studies were carried out using two PET/CT scanners (Aquiduo; Toshiba Medical Systems, Tochigi, Japan or Biograph 16; Siemens, Knoxville, TN, USA) with lutetium oxyorthosilicate crystals and 16-detector-row CT. For FAZA, PET/CT of the chest (CT followed by PET) was carried out 1 h after administration (mean administrative dose, 355 MBq), and 2 h later, a whole-body scan was carried out. For FDG, after at least 4 h of fasting, FDG was administered (mean, 261 MBq), and 1 h later, a whole-body scan was carried out. Immediately before the administration of FDG, blood was obtained to measure blood glucose levels. Images of the chest (for FAZA 1 h) and the whole body from the skull to the femur (for FAZA 2 h and FDG) were reconstructed using an ordered subset expectation maximization algorithm with CT-based attenuation correction. No i.v./oral contrast was used for CT acquisition. Two PET/CT scanners were calibrated using the same phantom, and cross-calibration factors were determined to ensure that the two scanners yielded comparable quantitative values.

Clinical and PET parameters. Regarding clinical parameters, patient information including age, sex, histology, clinical stage, T-stage, N-stage, and initial treatment method was collected. ¹⁸F-fluorodeoxyglucose tumor uptake was evaluated by measuring the maximum standardized uptake value (SUVmax) in the primary lung tumor (FDG Pr SUVmax) and in lymph node (LN) metastasis (FDG LN SUVmax). Two patients who showed blood glucose levels exceeding 150 mg/dL were excluded from the analysis of FDG parameters. The FAZA tumor uptake was evaluated by the tumor-to-muscle ratio (T/M), which was calculated by dividing SUVmax in the primary tumor or LN by SUVmean in back muscles in the same slice of the lesion at 1 and 2 h after administration (FAZA Pr T/M 1 h, FAZA Pr T/M 2 h, FAZA LN T/M 1 h, and FAZA LN T/M 2 h). In case of multiple LN metastases, the LN displaying the highest probe uptake was selected.

Data analyses. First, correlations among FDG and FAZA parameters were analyzed. Then, patients were divided into two groups, depending on the development of disease progression, and clinical and PET parameters were compared between

these two groups. Finally, the prognostic value of clinical and PET parameters was evaluated regarding progression-free survival (PFS) and overall survival (OS) for all patients and for stage III patients receiving chemoradiotherapy (CRT). The PET parameters for primary lesions were evaluated in 37 patients with T1–T4 stage excluding one T0 patient, and those for LN metastases were evaluated in 36 patients with N1–N3 stage excluding two N0 patients.

Statistical analyses were carried out using SPSS Statistics (version 21; IBM Japan, Tokyo, Japan). The correlation among FAZA and FDG uptake parameters was evaluated by obtaining Pearson's product moment correlation coefficient. For the comparison of patients who showed disease progression and those who did not exhibit disease progression, Mann–Whitney's *U*-test or the χ^2 -test/Fisher's exact test was used, depending on the type of parameter. For the survival analyses, Cox's proportional hazard model was used for univariate and multivariate analyses. For the continuous parameters, median values were used as cut-off values. Parameters judged as significant by Cox's analyses were further applied for Kaplan–Meier analysis with the log-rank test. *P*-values of <0.05 were considered statistically significant.

Results

Patient characteristics. Among 42 patients, four patients were excluded from the analysis as follows: colon cancer was detected in one patient resulting in a delay in the treatment of lung cancer, a diagnosis of NSCLC was denied in two patients (small-cell lung cancer in one patient and metastasis from endometrial cancer in another patient), and FAZA PET/CT could not be performed in the last patient. Patients underwent PET/CT using FAZA and FDG on separate days, with FDG PET/CT performed earlier in 31 patients and FAZA PET/CT performed earlier in seven patients; the mean interval was 4 days. The follow-up period from the start of treatment ranged from 13 to 234 weeks for all patients and from 37 to 234 weeks for survivors. Fifteen patients were upstaged by the staging work-up, resulting in 12 stage IIIA patients, 11 stage IIIB patients, and 15 stage IV patients. Thirty patients experienced disease progression (local recurrence, 17 patients; recurrence of LN metastasis, 14 patients; distant metastasis, 21 patients) with 17 patients having multiple sites of recurrence. Eighteen patients died, with all deaths attributable to lung cancer. Table 1 summarizes the characteristics of the 38 patients included in the analysis.

Correlation among FAZA and FDG uptake parameters. Results of correlation analyses are summarized in Table 2. There was no significant correlation between FAZA and FDG uptake in the primary lesion, whereas a strong correlation was observed between FAZA Pr T/M 1 h and FAZA Pr T/M 2 h ($r = 0.860$, $P < 0.001$). There was a moderate correlation between FAZA and FDG uptake in LN metastases (FAZA LN T/M 1 h vs. FDG LN SUVmax, $r = 0.437$, $P = 0.012$; FAZA LN T/M 2 h vs. FDG LN SUVmax, $r = 0.493$, $P = 0.004$) and a strong correlation between FAZA LN T/M 1 h and FAZA LN T/M 2 h ($r = 0.872$, $P < 0.001$). When uptake in the primary lesion was compared with that in LN metastasis within the same patient, a weak correlation was observed between FAZA Pr T/M 1 h and FAZA LN T/M 1 h ($r = 0.370$, $P = 0.034$), but no significant correlation was

Table 1. Characteristics of patients with advanced non-small-cell lung cancer (n = 38) according to disease progression

Parameter	Total	Progression		P-value
		Yes	No	
Age, years				
Median	67	67.5	65.5	0.788
Range	41–77	41–77	53–73	
Sex				
Male	28	22	6	0.652
Female	10	8	2	
Histology				
Adeno	19	13	6	0.189
SCC	11	9	2	
LC	8	8	0	
Clinical stage				
IIIA	12	8	4	0.539
IIIB	11	9	2	
IV	15	13	2	
T-stage				
T0	1	0	1	0.459
T1	6	5	1	
T2	14	12	2	
T3	6	5	1	
T4	11	8	3	
N-stage				
N0	2	0	2	0.094
N1	1	1	0	
N2	18	15	3	
N3	17	14	3	
FDG Pr SUVmax				
Median	11.12	11.12	13.38	0.433
Range	3.40–33.15	4.34–17.75	3.40–33.15	
FDG LN SUVmax				
Median	9.07	9.18	8.16	0.928
Range	2.91–18.92	2.91–18.92	4.49–16.50	
FAZA Pr T/M 1 h				
Median	1.72	1.77	1.54	0.280
Range	0.78–2.61	0.85–2.61	0.78–1.99	
FAZA Pr T/M 2 h				
Median	2.03	2.12	1.85	0.084
Range	0.81–3.33	0.84–3.33	0.81–2.35	
FAZA LN T/M 1 h				
Median	1.59	1.63	1.41	0.175
Range	1.08–2.28	1.08–2.28	1.19–2.18	
FAZA LN T/M 2 h				
Median	1.85	1.88	1.64	0.142
Range	1.04–2.83	1.10–2.83	1.04–2.39	

FAZA LN T/M, ¹⁸F-fluoroazomycin arabinoside lymph node tumor-to-muscle ratio; FAZA Pr T/M, ¹⁸F-fluoroazomycin arabinoside primary lung tumor-to-muscle ratio; FDG LN SUVmax, ¹⁸F-fluorodeoxyglucose lymph node tumor maximum standardized uptake value; FDG Pr SUVmax, ¹⁸F-fluorodeoxyglucose primary lung tumor maximum standardized uptake value; LC, large cell carcinoma; SCC, squamous cell carcinoma.

observed for other combinations (FAZA Pr T/M 2 h vs. FAZA LN T/M 2 h; FDG Pr SUVmax vs. FDG LN SUVmax).

Clinical and PET parameters in patients with/without disease progression. When clinical parameters were compared between patients who experienced disease progression and those who did not, no parameter was significantly different between the two groups. Although five PET parameters, excluding FDG Pr

SUVmax, showed higher median values in patients with disease progression than those without disease progression, the differences were not statistically significant (Table 1).

Survival analyses in all patients. The prognostic value of clinical and PET parameters was first evaluated in all patients (Table 3). In the univariate analyses, clinical stage (stage III vs. IV, hazard ratio [HR] = 2.43, *P* = 0.021), FAZA LN T/M 1 h (cut-off, 1.59; HR = 2.50; *P* = 0.028), and FAZA LN T/M 2 h (cut-off, 1.85; HR = 3.80; *P* = 0.002) were significant predictors of PFS. Multivariate analysis was then carried out for these three parameters. As there was a strong correlation between FAZA LN T/M 1 h and FAZA LN T/M 2 h (*r* = 0.872), these two parameters were assessed separately to avoid multicollinearity. In a model with FAZA LN T/M 1 h, clinical stage (HR = 2.46; *P* = 0.029) and FAZA LN T/M 1 h (HR = 2.89; *P* = 0.014) were statistically significant predictors, and in a model with FAZA LN T/M 2 h, clinical stage (HR = 4.06; *P* = 0.002) and FAZA LN T/M 2 h (HR = 6.67; *P* < 0.001) were statistically significant predictors (Table 4). Kaplan–Meier analyses with log–rank tests undertaken for these parameters indicated that patients with stage IV, patients with FAZA LN T/M 1 h > 1.59 and patients with FAZA LN T/M 2 h > 1.85 showed significantly worse PFS than those with stage III, with FAZA LN T/M 1 h ≤ 1.59 and with FAZA LN T/M 2 h ≤ 1.85 (*P* = 0.017, 0.023, and 0.001, respectively) (Fig. 1).

In the univariate analysis for OS, no parameters showed *P*-values < 0.05, with FAZA LN T/M 1 h displaying the lowest *P*-value (*P* = 0.059).

Survival analyses in stage III/CRT patients. The prognostic value of clinical and PET parameters was then evaluated in stage III patients treated with concurrent or sequential CRT (Table 5). Univariate analysis illustrated that only FAZA LN T/M 2 h was a significant predictor of PFS (cut-off, 1.85; HR = 4.16; *P* = 0.025). Kaplan–Meier analysis with log–rank test indicated that patients with FAZA LN T/M 2 h > 1.85 showed significantly worse PFS than those with FAZA LN T/M 2 h ≤ 1.85 (*P* = 0.016) (Fig. 2).

In the univariate analysis for OS, no parameters showed *P*-values < 0.05, with FAZA LN T/M 1 h displaying the lowest *P*-value (*P* = 0.050).

Discussion

In the present prospective study, the prognostic value of FAZA PET/CT carried out before treatment in patients with advanced NSCLC was evaluated in comparison with FDG PET/CT. Although FMISO has been widely applied for patients with various types of cancer, its application for patients with NSCLC is relatively limited, with only a few reports published on its prognostic value.^(19,20)

First, patients were divided in two groups, patients who experienced disease progression and those who did not, and clinical and PET parameters were compared. However, no parameters showed significant difference between these two groups. As for the initial site of recurrence, patients with recurrence in primary tumor showed higher FAZA Pr T/M 2 h than those with recurrence in other sites (LN or distant metastasis) and patients with recurrence in LN metastases showed higher FAZA LN T/M 2 h than patients with recurrence in other sites, but these differences were not statistically significant (data not shown).

Univariate analyses on all patients (Cox's proportional hazards model and Kaplan–Meier analysis with the log–rank test)

illustrated that three parameters, clinical stage, FAZA LN T/M 1 h, and FAZA LN T/M 2 h, were significant predictors of PFS. Furthermore, multivariate analysis indicated that these three parameters are independent prognostic indicators. Among three parameters, FAZA LN T/M 2 h showed the lowest *P*-value and highest HR, indicating that this parameter had the strongest prognostic value.

In the present study, among 38 enrolled patients, 15 patients were upstaged to stage IV because of the detection of unexpected metastases. Because stage IV patients were heterogeneous regarding the site of metastases and the initial treatment methods, additional analyses were carried out for a relatively uniform subgroup of patients, namely stage III patients treated by concurrent or sequential CRT (12 patients and 8 patients,

Table 2. Correlation among various ¹⁸F-fluoroazomycin arabinoside (FAZA) and ¹⁸F-fluorodeoxyglucose (FDG) uptake parameters in patients with advanced non-small-cell lung cancer (*n* = 38)

	FDG Pr SUVmax	FDG LN SUVmax	FAZA Pr T/M 1 h	FAZA Pr T/M 2 h	FAZA LN T/M 1 h	FAZA LN T/M 2 h
FDG Pr SUVmax		<i>r</i> = 0.042 <i>P</i> = 0.815	<i>r</i> = 0.325 <i>P</i> = 0.061	<i>r</i> = 0.323 <i>P</i> = 0.059	N/D	N/D
FDG LN SUVmax	<i>r</i> = 0.042 <i>P</i> = 0.815		N/D	N/D	<u><i>r</i> = 0.437</u> <u><i>P</i> = 0.012</u>	<u><i>r</i> = 0.493</u> <u><i>P</i> = 0.004</u>
FAZA Pr T/M 1 h	<i>r</i> = 0.325 <i>P</i> = 0.061	N/D		<u><i>r</i> = 0.860</u> <u><i>P</i> < 0.001</u>	<u><i>r</i> = 0.370</u> <u><i>P</i> = 0.034</u>	N/D
FAZA Pr T/M 2 h	<i>r</i> = 0.323 <i>P</i> = 0.059	N/D	<u><i>r</i> = 0.860</u> <u><i>P</i> < 0.001</u>		N/D	<i>r</i> = 0.272 <i>P</i> = 0.119
FAZA LN T/M 1 h	N/D	<u><i>r</i> = 0.437</u> <u><i>P</i> = 0.012</u>	<u><i>r</i> = 0.370</u> <u><i>P</i> = 0.034</u>	N/D		<u><i>r</i> = 0.872</u> <u><i>P</i> < 0.001</u>
FAZA LN T/M 2 h	N/D	<u><i>r</i> = 0.493</u> <u><i>P</i> = 0.004</u>	N/D	<i>r</i> = 0.272 <i>P</i> = 0.119	<u><i>r</i> = 0.872</u> <u><i>P</i> < 0.001</u>	

Combinations showing significant correlations are underlined. FAZA LN T/M, FAZA arabinoside lymph node tumor-to-muscle ratio; FAZA Pr T/M, FAZA primary lung tumor-to-muscle ratio; FDG LN SUVmax, FDG lymph node tumor maximum standardized uptake value; FDG Pr SUVmax, FDG primary lung tumor maximum standardized uptake value; N/D, analysis not done.

Table 3. Univariate analyses of clinical and PET parameters for progression-free and overall survival in all patients advanced non-small-cell lung cancer (*n* = 38)

Parameter	Progression-free survival			Overall survival		
	HR	95% CI	<i>P</i> -value	HR	95% CI	<i>P</i> -value
Age >67 vs ≤67	0.96	0.46–2.00	0.919	0.81	0.32–2.08	0.666
Sex Male versus female	0.73	0.31–1.72	0.477	0.88	0.31–2.48	0.812
Histology Adeno versus SCC/LC	1.26	0.60–2.62	0.543	1.26	0.50–3.21	0.624
Clinical stage III versus IV	2.43	1.14–5.15	0.021	2.35	0.93–5.99	0.072
T-stage T0–2 versus T3–4	0.97	0.46–2.06	0.946	0.97	0.37–2.51	0.946
N-stage N0–2 versus N3	1.91	0.91–4.01	0.087	2.49	0.96–6.45	0.061
FDG Pr SUVmax >11.12 vs ≤11.12	1.05	0.49–2.25	0.904	0.62	0.23–1.67	0.346
FDG LN SUVmax >9.07 vs ≤9.07	1.69	0.78–3.66	0.180	1.79	0.69–4.63	0.230
FAZA Pr T/M 1 h >1.72 vs ≤1.72	1.81	0.86–3.82	0.120	2.27	0.86–5.98	0.096
FAZA Pr T/M 2 h >2.03 vs ≤2.03	2.00	0.96–4.18	0.065	1.88	0.73–4.87	0.192
FAZA LN T/M 1 h >1.59 vs ≤1.59	2.50	1.11–5.62	0.028	2.72	0.96–7.70	0.059
FAZA LN T/M 2 h >1.85 vs ≤1.85	3.80	1.65–8.75	0.002	2.15	0.83–5.61	0.116

Adeno, adenocarcinoma; CI, confidence interval; FAZA LN T/M, ¹⁸F-fluoroazomycin arabinoside lymph node tumor-to-muscle ratio; FAZA Pr T/M, ¹⁸F-fluoroazomycin arabinoside primary lung tumor-to-muscle ratio; FDG LN SUVmax, ¹⁸F-fluorodeoxyglucose lymph node tumor maximum standardized uptake value; FDG Pr SUVmax, ¹⁸F-fluorodeoxyglucose primary lung tumor maximum standardized uptake value; HR, hazard ratio; LC, large cell carcinoma; SCC, squamous cell carcinoma.

Table 4. Multivariate analyses for progression-free survival in patients with advanced non-small-cell lung cancer (n = 38)

Parameter	Model with FAZA LN T/M 1 h			Model with FAZA LN T/M 2 h		
	HR	95% CI	P-value	HR	95% CI	P-value
Clinical stage III versus IV	2.46	1.10–5.53	0.029	4.06	1.66–9.96	0.002
FAZA LN T/M 1 h >1.59 vs ≤1.59	2.89	1.24–6.72	0.014			
FAZA LN T/M 2 h >1.85 vs ≤1.85				6.67	2.54–17.48	<0.001

CI, confidence interval; FAZA LN T/M, ¹⁸F-fluoroazomycin arabinoside lymph node tumor-to-muscle ratio; HR, hazard ratio.

respectively). All concurrent CRT patients received cisplatin-based combination chemotherapy. Seven sequential CRT patients received carboplatin-based combination chemotherapy, and one patient received cisplatin-based combination chemotherapy. The subgroup analyses indicated that FAZA LN T/M 2 h was the only significant predictor of PFS. Clinical stage (stage IIIA vs. IIIB) and initial treatment (concurrent CRT vs. sequential CRT) were not significant parameters. Although the number of patients was relatively small and an additional study with a larger number of patients is needed, the present study suggests the pretreatment FAZA uptake in LN metastases can predict treatment outcome of CRT for stage III patients.

In contrast to PFS, no significant predictive factors were depicted with regard to OS with FAZA LN T/M 1 showing relatively low values. In patients who experienced disease progression after first-line treatment, second-line treatment was variable according to the type of recurrence, and the prognoses may largely depend on the effectiveness of the second-line treatment. This may somewhat decrease the prognostic power of clinical and PET parameters for OS.

The present study indicated that the uptake of FAZA in the primary lesion was not a significant prognostic factor. One possibility is that, in the case of advanced NSCLC having LN metastases, more aggressive cancer cells were selected during the process of metastasis to LNs, and the presence of more aggressive cancer cells in LN metastases was related to the poorer prognosis. There was no strong correlation between FAZA and FDG uptake in the primary lesion and that in LN metastasis, suggesting the different nature of the primary lesion and LN metastasis in individual patients. In the present study, PET parameters for primary lesions were evaluated in 37 patients. As 35 out of these 37 patients also had LN metastases, it is likely that the aggressive properties of LN metastases affected patients' prognoses more than did primary

lesions. These results suggest the importance of the characterization of LN metastases in addition to primary lesions in patients with advanced NSCLC.

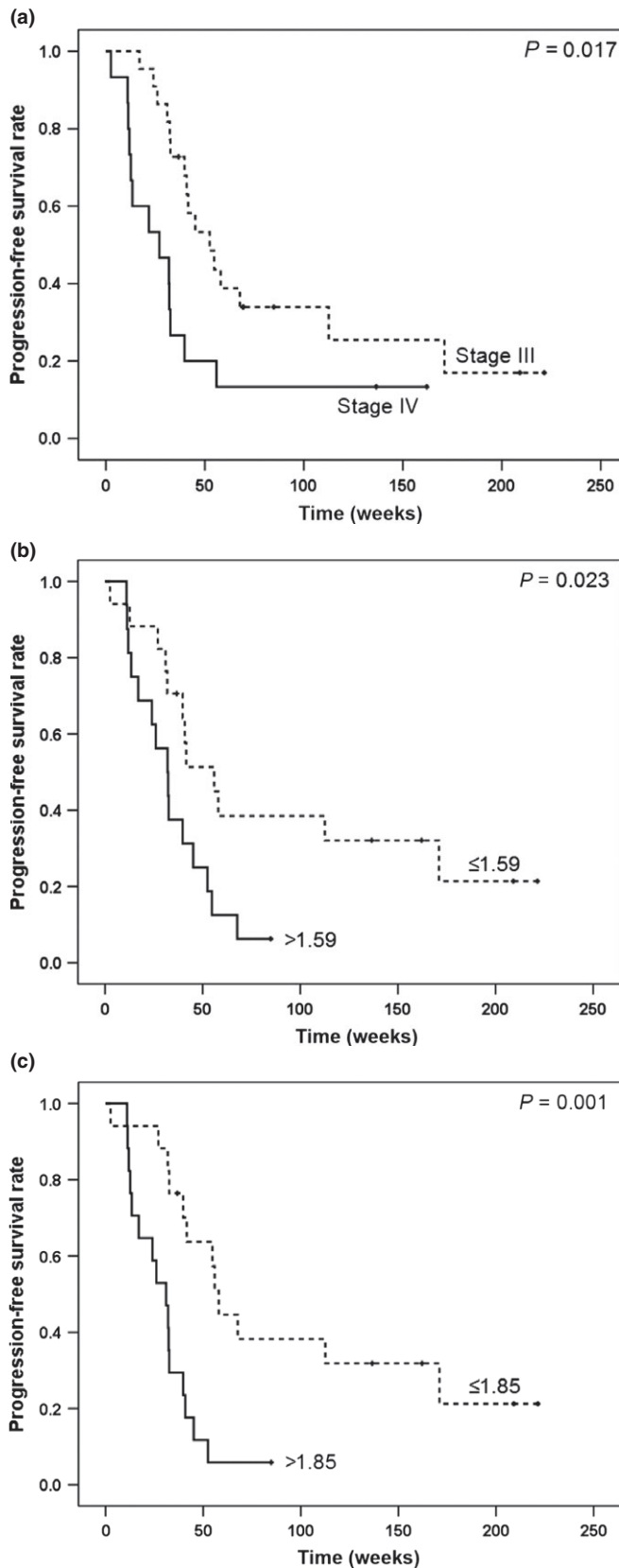


Fig. 1. Kaplan–Meier curves of progression-free survival in patients with advanced non-small-cell lung cancer according to clinical stage (a) and tumor uptake of ¹⁸F-fluoroazomycin arabinoside (b,c). ¹⁸F-fluoroazomycin arabinoside tumor uptake was evaluated by the tumor-to-muscle ratio, which was calculated by dividing the maximum standardized uptake value in the lymph node by the mean standardized uptake value in back muscles in the same slice of the lesion 1 h (b) and 2 h (c) after administration.

Table 5. Univariate analyses of clinical and PET parameters for progression-free survival (PFS) and overall survival (OS) in stage III patients treated with chemoradiotherapy (*n* = 23)

Parameter	Progression-free survival			Overall survival		
	HR	95% CI	<i>P</i> -value	HR	95% CI	<i>P</i> -value
Age, years >65.5 vs ≤65.5	1.26	0.43–3.71	0.676	2.22	0.36–13.80	0.393
Sex Male versus female	0.73	0.23–2.35	0.599	0.33	0.04–3.00	0.326
Histology Adeno versus SCC/LC	1.78	0.61–5.16	0.286	1.06	0.17–6.49	0.948
Clinical stage IIIA versus IIIB	2.44	0.84–7.09	0.100	3.04	0.50–18.53	0.227
T-stage T0–2 versus T3–4	1.76	0.56–5.57	0.336	2.39	0.14–39.71	0.543
N-stage N0–2 versus N3	1.99	0.68–5.80	0.207	3.17	0.52–19.21	0.209
Initial treatment conc. CRT versus seq CRT	0.79	0.26–2.36	0.673	0.86	0.14–5.21	0.869
FDG Pr SUVmax >11.60 vs ≤11.60	1.06	0.34–3.25	0.926	0.55	0.06–4.99	0.595
FDG LN SUVmax >9.00 vs ≤9.00	1.94	0.64–5.85	0.238	1.89	0.31–11.41	0.488
FAZA Pr T/M 1 h >1.50 vs ≤1.50	1.03	0.34–3.10	0.961	0.80	0.13–4.81	0.805
FAZA Pr T/M 2 h >1.95 vs ≤1.95	1.62	0.56–4.65	0.374	1.50	0.24–9.45	0.667
FAZA LN T/M 1 h >1.55 vs ≤1.55	3.14	0.90–10.99	0.073	9.47	1.00–90.0	0.050
FAZA LN T/M 2 h >1.85 vs ≤1.85	4.16	1.20–14.39	0.025	5.56	0.61–50.4	0.127

Adeno, adenocarcinoma; CI, confidence interval; conc. CRT, concurrent chemoradiotherapy; FAZA LN T/M, ¹⁸F-fluoroazomycin arabinoside lymph node tumor-to-muscle ratio; FAZA Pr T/M, ¹⁸F-fluoroazomycin arabinoside primary lung tumor-to-muscle ratio; FDG LN SUVmax, ¹⁸F-fluorodeoxyglucose lymph node tumor maximum standardized uptake value; FDG Pr SUVmax, ¹⁸F-fluorodeoxyglucose primary lung tumor maximum standardized uptake value; HR, hazard ratio; LC, large cell carcinoma; SCC, squamous cell carcinoma; seq. CRT, sequential chemoradiotherapy.

¹⁸F-fluoroazomycin arabinoside was designed to have faster kinetics than FMISO. In the present study, FAZA uptake parameters at 1 and 2 h were evaluated and FAZA LN T/M 2 h showed the best performance with regard to the prediction of PFS. Although it is not possible to determine the optimal time point to assess FAZA uptake parameters from the present data alone, the present study indicated that FAZA uptake parameters assessed at 2 h post-administration can afford clinically useful information.

In contrast to FAZA, FDG uptake parameters were not significant predictors in the present study. Bollineni *et al.* compared FAZA and FDG PET in 11 patients with stage III–IV NSCLC and found different distribution patterns of FAZA and FDG in primary lesions. In addition, no significant correlation was observed between FAZA and FDG uptake.⁽¹⁵⁾ The present study also uncovered no significant correlation between FAZA and FDG uptake in primary lesions. As for LN metastasis, although a significant correlation was observed in the uptake of FAZA and FDG, the correlation coefficient was not high. These results suggest that the meaning of the uptake of each probe by the lesion is not identical. There are many reports describing that FDG uptake in the primary lesion is a prognostic indicator of NSCLC. However, many reports focused on operable and/or early-stage (stage I–II) patients.^(21–23) The prognostic value of FDG uptake in patients with advanced NSCLC is controversial and further studies are necessary.^(24–26)

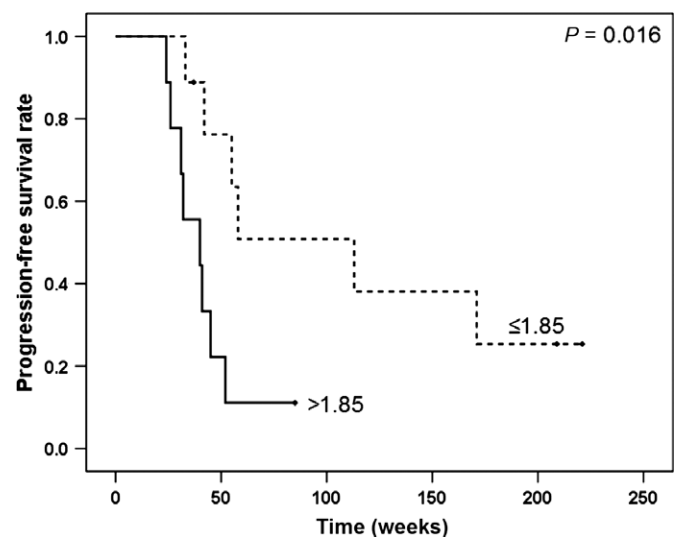


Fig. 2. Kaplan–Meier curves of progression-free survival in patients with stage III non-small-cell lung cancer treated by chemoradiotherapy, according to tumor uptake of ¹⁸F-fluoroazomycin arabinoside. Tumor uptake was evaluated by the tumor-to-muscle ratio, which was calculated by dividing the maximum standardized uptake value in the lymph node by the mean standardized uptake value in back muscles in the same slice of the lesion 2 h after administration.

There are several limitations in the present study. First, the number of patients was not sufficient to yield strong statistical power. Second, we were unable to undertake analyses including the volume information. Recently, there have been reports on the utility of adding volume information to the PET quantitative evaluation, in which the metabolic tumor volume and total lesion glycolysis measured by FDG PET/CT were strong predictors of prognosis in patients with NSCLC.^(27,28) The capability of FDG-PET/CT may have been underestimated in the present study.

In conclusion, although the number of patients is not large enough, the present study indicated for the first time that pre-treatment FAZA uptake in LN metastases was a strong and independent predictor of PFS, in patients with advanced NSCLC treated non-surgically. Especially in stage III patients receiving CRT, FAZA uptake in LN metastases 2 h post-administration can predict the outcome of CRT. The present

results warrant further clinical studies with larger numbers of NSCLC patients.

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Disclosure Statement

The authors have no conflict of interest.

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