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RESEARCH ARTICLE

A Pilot Study of Texture Analysis of Primary Tumor [^{18}F]FDG Uptake to Predict Recurrence in Surgically Treated Patients with Non-small Cell Lung Cancer

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Abstract

Purpose: To examine whether the heterogeneous texture parameters in primary tumor can predict prognosis of patients with non-small cell lung cancer (NSCLC) received surgery after 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) positron emission tomography (PET)/X-ray computed tomography (CT).

Procedure: This retrospective study included 55 patients with NSCLC who underwent [^{18}F]FDG-PET/CT before surgery from January 2011 and December 2015. SUV-related (SUVmax and SUVmean), volumetric (metabolic tumor volume [SUV ≥ 2.5], and total lesion glycolysis) and texture parameters (local parameters; entropy, homogeneity, and dissimilarity and regional parameters; intensity variability [IV], size-zone variability [SZV], and zone percentage [ZP]) were obtained. Tumor size, TNM stage, SUV-related, volumetric, and texture parameters were compared between the patients with progression and without progression using Mann-Whitney's U or χ^2 test and progression-free survival (PFS) and prognostic significance were assessed by Kaplan-Meier method and Cox regression analysis, respectively.

Results: Nineteen patients eventually showed progression, and 36 patients were alive without progression during clinical follow-up (median follow-up PFS; 23 months [range, 1–71]). The patients with progression showed significantly larger tumor size ($p < 0.001$), higher IV ($p = 0.010$), and higher SZV ($p = 0.007$) than those without progression. PFS was significantly shorter in patients with large tumor size ($p = 0.008$), high T stage ($p = 0.009$), high stage ($p = 0.013$), high IV ($p = 0.012$), and high SZV ($p = 0.015$) at univariate analysis. At multivariate analysis, stage (hazard ratio [HR] 1.62, $p = 0.035$) and IV (hazard ratio 6.19, $p = 0.048$) were only remained independent predictors for PFS.

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Conclusions: The regional heterogeneity texture parameters IV and SZV can predict tumor progression, and IV has the potential to predict prognosis of surgically treated NSCLC patients.

Key Words: Non-small cell lung cancer, [^{18}F]FDG-PET/CT, SUV, Texture analysis

Introduction

Lung cancer is the first leading cause of cancer deaths in males and the second in females worldwide, and most lung cancers (80–85 %) are non-small cell lung cancers (NSCLCs) [1, 2]. Recently, the incidence of early-stage NSCLC has increased as a result of the application of low-dose X-ray computed tomography (CT) screening and improved cures using standard surgery [3]. However, in spite of improved surgical resections and advanced adjuvant therapies, the 5-year survival rates after resection of localized NSCLC were only approaching 50 % [4, 5]. The TNM stage has been reported as the primary prognostic factor in NSCLC. However, there are the differences in the tumor and patient specific factors in the same stage, which make a heterogeneous population of patients [6, 7]. Therefore, it is necessary to seek other prognostic factors besides TNM stages to identify patients at high risk for recurrence, predict prognosis, and recommend individualized adjuvant therapy [8].

Uptake of the glucose analogue 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG) represents glucose metabolic activity and is widely used as a tracer of positron emission tomography (PET)/CT in oncology [9]. Recently, PET image texture analysis was proposed to characterize the heterogeneity of tumor [^{18}F]FDG uptake [10]. There are close relationships between tumor heterogeneity and cellular proliferation, necrosis, hypoxia, or angiogenesis, all of which might affect the treatment response and prognosis in many type of cancers [11, 12]. The [^{18}F]FDG-PET texture features have been reported as the useful markers for predicting treatment response and prognosis in esophageal cancer [13]. There were also several studies which examined the [^{18}F]FDG-PET textural features for prediction of prognosis for NSCLC in various staged and treated populations [14–20]. However, to our knowledge, the prognostic role of pretreatment [^{18}F]FDG-PET textural features in surgically resected NSCLC has not been reported. If such parameters are present before therapy, they will contribute to decide the therapeutic strategy, such as neoadjuvant or adjuvant chemotherapy or determine the follow-up protocol.

The present study was performed to examine whether the heterogeneous texture parameters in primary tumor can predict prognosis of patients with NSCLC received surgery after [^{18}F]FDG-PET/CT.

Materials and Methods

Patients

This retrospective study was approved by the institutional review board, and the need to obtain informed consent was waived. The inclusion criteria for the study were as follows: (1) the patients with NSCLC who underwent [^{18}F]FDG-PET/CT before surgery from January 2011 and December 2015 and (2) the primary tumor had visible uptake on the PET/CT reports. Following patients were excluded: (1) whose primary tumor metabolic tumor volumes (MTVs) $\leq$ 10.0 cm^3 with a threshold standardized uptake value (SUV) of $\geq$2.5, (2) who had a previous history of surgery, chemotherapy, or radiotherapy for lung cancer or other malignancy, and (3) whose clinical or follow-up data were incomplete.

Imaging Protocols

Instruction of pre-PET/CT fast for $\geq$5 h resulted in the mean plasma glucose level of 105 (range, 74–169) mg/day just before [^{18}F]FDG intravenous injection.

The whole body PET/CT from brain to feet (acquisition time; 2.5 min per bed position, 14 bed positions) was performed after 16-slice CT scanning (slice thickness, 3.75 mm; pitch, 1.75 mm; 120 keV; auto mA (35–100 mA depending on patient body mass)) using a Discovery 600M PET/CT (GE Medical Systems, Milwaukee, WI, USA) 1 h after [^{18}F]FDG (median 196.9 (interquartile range, 176.4–220.0) MBq) injection. The CT attenuation corrected acquired data were reconstructed using a three-dimensional ordered-subset expectation maximization algorithm (image matrix size, 192 × 192; 16 subsets, 2 iterations: VUE Point Plus). The PET transaxial spatial resolution was 5.1-mm full-width half-maximum (FWHM) in-plane.

Image Analysis

Two radiologists who knew the study purpose but were blinded to clinical and pathological information confirmed independently that the primary lesion had visible uptake (equal to or more than mediastinum) [21]. The third radiologist assessed visible primary tumor parameters. The volume of interest (VOI) was set manually with care for excluding the adjacent physiological [^{18}F]FDG-avid

structures, and then tumor boundaries were automatically contoured. MTV was defined as the tumor volume (cm^3) with an SUV ≥ 2.5, and the intra-tumor-areas with SUV of < 2.5 were not included in MTV [22]. SUVmax and SUVmean were defined as the maximum and mean tissue activity divided by the injected dose and corrected for the per gram of body weight, respectively. Total lesion glycolysis (TLG) was the SUVmean multiplied by the MTV. The software (Advantage Windows Workstation; GE Healthcare, Milwaukee, WI) provided SUVmax, SUVmean, and MTV automatically.

Textual Analysis

The three robust local heterogeneity parameters (entropy, homogeneity, and dissimilarity) and three robust regional parameters (intensity variability (IV), size-zone variability (SZV), and zone percentage (ZP)) were selected for the textual analysis [13]. The rescaling was performed with the minimum to the maximum intensity range of each VOI using 64 discrete values to measure the tumor heterogeneity. The PET images were post-filtered with a 5.1-mm FWHM Gaussian filter to reduce noise; thus, small variations can be regarded as representing heterogeneity [23]. Because the textual features are affected by the tumor volume, especially those ≤ 10 cm^3, the textural analyses were only performed for MTVs > 10 cm^3 [15]. The program for calculating these six parameters was implemented using Python computer language and executed on Mac OS X 10.11.3 with an Intel Core i7 (2.3 GHz) CPU and 4-GB memory.

Histological Analyses and Staging

Radical surgery was performed from 7 to 93 days (mean, 46 days) after [^{18}F]FDG-PET/CT. Primary lesions and the dissected pulmonary and mediastinal nodes were examined histologically. Tumor size was the largest diameter of the resected tumor. Staging was performed by the revised TNM staging system for lung cancer [24].

Follow-up of Patients

Medical records provided information on patients' prognoses. The last follow-up was conducted in December 2017. The progression of disease was evaluated based on clinical and imaging follow-up information. Follow-up was performed every 2–3 months from surgery during the first 2 years and every 6–12 months thereafter. Progression-free survival (PFS) was defined as the time from the initiation of therapy to the date of progressive disease, death, or last follow-up, whichever occurred first.

Statistical Analysis

The Mann-Whitney *U*, chi-squared, or Fisher's exact test were used to assess the differences between two quantitative variables or compare categorical data, appropriately. Areas under the receiver-operating-characteristic (ROC) curves (AUCs) were calculated to estimate the diagnostic accuracy in predicting disease progression. The Kaplan-Meier method was used to develop survival curves and which were compared using the log-rank test. The data were dichotomized by the median value of each [^{18}F]FDG-parameter for PFS. Hazard ratios (HRs) were calculated by the Cox regression analysis using these dichotomized values. Multivariate Cox regression analysis was performed to identify the independent factors using the variables that were significant at univariate analysis.

Data were presented as medians and interquartile ranges. A value of $p < 0.05$ was considered as statistically significant, and all p values presented were two-sided. The MedCalc Statistical Software (MedCalc Software, Mariakerke, Belgium) was used for statistical analyses.

Results

Patient and Tumor Characteristics

Of the 104 patients who had a visible primary tumor, 17 patients were excluded, 10 had other malignancy, and 7 lacked follow-up information. Among 87 patients (68 males, 19 females [mean age, 69 years; range, 35–87 years]), 32 patients showed a tumor of MTV ≤ 10.0 cm^3. Although these 32 patients were excluded for the texture analysis, other analyses except for texture parameters were performed for all these 87 patients as the supplemental analysis.

Finally, 55 patients were eligible for analysis (Table 1): 43 males and 12 females; mean age 69 (range, 35–87) years; 28 adenocarcinomas, 22 squamous cell carcinomas (SCCs), and 5 other carcinomas (2 adenosquamous carcinomas, 1 giant cell carcinoma, 1 mucoepidermoid carcinoma, and 1 pleomorphic carcinoma); 15 well differentiated, 28 moderately differentiated, 9 poorly differentiated, and 3 undifferentiated carcinomas; 48 (87 %) patients with T1 or T2 primary lesions, 15 (27 %) patients with nodal metastases (7 N1 and 8 N2), and no patients with distant metastasis; 13 stage IA, 19 stage IB, 9 stage IIA, 4 stage IIB, 9 stage IIIA, and 1 stage IIIB patients. Twenty seven (3 stage IA, 10 stage IB, 6 stage IIA, 3 stage IIB, and 5 stage IIIA) patients received post-operative adjuvant chemotherapy; 13 tegafur-uracil (UFT) and 14 platinum-doublet chemotherapies (5 cisplatin (CDDP)/inorelbine (VNR), 3 carboplatin (CBCDA)/paclitaxel (PTX), 2 CBCDA/gemcitabine (GEM), and each one of CDDP/TS-1, CDDP + GEM, CBCDA/pemetrexed (PEM), and CBCDA/TS-1).

Table 1. Characteristics of 55 NSCLC patients with $MTV_{2.5} > 10.0$ cm^3 received surgery

Characteristic	Progression	Non-progression	Total	*p* value
Number	19	36	55	
Sex				0.44
Male	16	27	43	
Female	3	9	12	
Location				0.43
Right upper lobe	7	12	19	
Right middle lobe	0	0	0	
Right lower lobe	4	5	9	
Left upper lobe	5	6	11	
Left lower lobe	3	13	16	
Histology				0.45
Adenocarcinoma	9	19	28	
Squamous cell carcinoma	7	15	22	
Others	3	2	5	
Differentiation				0.92
Well differentiated	5	10	15	
Moderately differentiated	9	19	28	
Poorly differentiated	4	5	9	
Undifferentiated	1	2	3	
Tumor status				0.009
T1	1	16	17	
T2	14	17	31	
T3	2	3	5	
T4	2	0	2	
Lymph node status				0.49
N0	12	28	40	
N1	3	4	7	
N2	4	4	8	
Stage				0.011
IA	1	12	13	
IB	7	12	19	
IIA	3	6	9	
IIB	2	2	4	
IIIA	5	4	9	
IIIB	1	0	1	
Post-operative adjuvant therapy				0.35
Not-performed	8	20	28	
Performed	11	16	27	

NSCLC, non-small cell lung cancer; $MTV_{2.5}$, metabolic tumor volume (MTV) with SUVs ≥ 2.5

Prediction of Progression

The patients with progression showed significantly higher T stage ($p = 0.009$), higher stage ($p = 0.011$), and larger tumor size ($p < 0.001$) than those without progression. Other clinicopathological factors did not reach the statistical significance in tumor progression (Tables 1 and 2). The same results were also observed in 87 patients (Suppl. Tables 1 and 2, see Electronic supplementary material [ESM]).

Comparison of [^{18}F]FDG-PET pretreatment parameters between progression and non-progression was shown in Table 2: Neither SUV-related nor volumetric-parameters were significantly different between progression and non-progression. The subgroup analysis was also performed according to the type of histology. Neither SUV nor volumetric parameters were significantly different between progression and non-progression in the adenocarcinoma group. In the SCC group, the patients with progression showed significantly higher TLG ($p = 0.041$) than those without progression, but no significant difference between progression and non-progression was seen in SUVmax, SUVmean, and MTV ($p > 0.05$, each) (Suppl. Tables 3 and 4; see ESM).

The additional supplemental analyses were also performed in all 87 patients to examine the difference in other volumetric parameters with a different threshold level ($MTV_{42\ \%}$ [MTV with SUVs ≥ 42 % of SUVmax] and $TLG_{42\ \%}$ [TLG with $MTV_{42\ \%}$]) between progression and non-progression for comparison with $MTV_{2.5}$ (MTV with SUVs ≥ 2.5) and $TLG_{2.5}$ (TLG with $MTV_{2.5}$). Although there were no significant differences in $MTV_{2.5}$ ($p = 0.16$) and $TLG_{2.5}$ ($p = 0.12$) between progression and non-progression patients, the patients with progression showed significantly higher $MTV_{42\ \%}$ ($p = 0.049$) and $TLG_{42\ \%}$ ($p = 0.043$) than those without progression (Suppl. Table 2; see ESM).

In the texture analysis, the patients with progression showed significantly higher IV ($p = 0.010$) and SZV ($p = 0.007$) than those without progression, but no significant difference between progression and non-progression was seen in entropy, homogeneity, dissimilarity and ZP ($p > 0.05$, each). In the adenocarcinoma group, the patients with progression showed significantly higher IV ($p = 0.021$) than those without progression, but no significant difference between progression and non-progression was seen in entropy, homogeneity, dissimilarity, SZV, and ZP ($p > 0.05$, each) (Suppl. Table 3; see ESM). In the SCC group, the patients with progression showed significantly higher IV ($p = 0.032$) and SZV ($p = 0.032$) than those without progression, but no significant difference between progression and non-progression was seen in entropy, homogeneity, dissimilarity, and ZP ($p > 0.05$, each) (Suppl. Table 4; see ESM).

The AUC for the ability to predict progression significantly were 0.78 for tumor size ($p < 0.001$), 0.72 for tumor status ($p < 0.001$), 0.70 for stage ($p = 0.004$), 0.71 for IV ($p = 0.004$), and 0.72 for SZV ($p = 0.003$) (Suppl. Tables 5; see ESM). Diagnostic performances of IV and SZV for prediction of progression are summarized in Suppl. Table 6 (see ESM). The accuracy to predict progression was 71 % for IV and 67 % for SZV, respectively. No significant differences in AUC were found among these parameters ($p > 0.05$ each). In the supplemental analyses except texture parameters for 87 patients, the AUC for the ability to predict progression significantly were 0.71 for tumor size ($p < 0.001$), 0.68 for tumor status ($p < 0.001$), 0.73 for stage ($p < 0.001$), 0.63 for $MTV_{42\ \%}$ ($p = 0.042$), and 0.63 for $TLG_{42\ \%}$ ($p = 0.031$), whereas no significant differences from the lines of references were seen for other parameters (Suppl. Table 7; see ESM).

Table 2. Comparison of age, tumor size and [^{18}F]FDG PET pretreatment parameters between progression and non-progression of 55 NSCLC patients with $MTV_{2.5} > 10.0$ cm^3 received surgery

Index	Progression patients ($n = 19$)			Non-progression patients ($n = 36$)			p value
	Median	IQR	Range	Median	IQR	Range	
Age	72	66–76.8	62–85	69	62.5–75	35–87	0.27
Size (mm)	40.0	32.8–43.8	29.0–65.0	30.0	28.5–35.0	27.0–60.0	< 0.001
SUVmax	11.5	7.9–14.1	2.8–32.2	9.3	6.3–14.8	3.0–37.2	0.37
SUVmean	5.0	4.0–6.8	2.6–9.7	4.2	3.5–6.0	2.7–12.4	0.19
$MTV_{2.5}$ (cm^3)	20.7	12.6–41.1	10.6–199.1	13.9	12.1–23.6	10.1–159.8	0.17
$MTV_{42\ \%}$ (cm^3)	11.2	5.7–13.4	3.8–72.6	7.0	3.9–13.5	1.4–62.5	0.066
$TLG_{2.5}$	102.7	53.2–245.2	29.1–1632.9	74.7	48.9–110.0	29.2–687.0	0.13
$TLG_{42\ \%}$	59.3	34.3–162.8	16.7–900.2	38.9	19.6–71.5	2.9–420.4	0.072
Entropy	7.28	7.14–7.50	6.34–7.63	7.15	7.04–7.32	5.91–7.57	0.052
Homogeneity	0.188	0.173–0.214	0.120–0.366	0.173	0.159–0.191	0.127–0.356	0.15
Dissimilarity	9.94	8.14–11.36	4.35–18.46	10.90	9.48–12.87	4.08–15.90	0.13
Intensity variability	10.40	5.98–17.73	3.70–62.20	6.65	4.20–8.50	2.90–69.60	0.010
Size-zone variability	217.30	159.10–404.38	79.40–1313.90	133.55	95.30–194.75	30.70–729.8	0.007
Zone percentage	0.34	0.20–0.42	0.12–0.72	0.41	0.35–0.53	0.01–0.83	0.053

NSCLC, non-small cell lung cancer; IQR, interquartile ranges; $MTV_{2.5}$, metabolic tumor volume (MTV) with SUVs ≥ 2.5; $MTV_{42\ \%}$, MTV with SUVs ≥ 42 % of SUVmax; $TLG_{2.5}$, total lesion glycolysis (TLG) with $MTV_{2.5}$; $TLG_{42\ \%}$ TLG with $MTV_{42\ \%}$
p values for comparison between low-risk and high-risk tumors (Mann-Whitney U test)

Survival Prediction

Nineteen patients showed eventually progression, and among them, six patients were died and 13 patients were alive. Thirty six patients were alive without progression during clinical follow-up. Median follow-up was 23.0 months (range, 1–71).

The results of long-rank test of clinical prognostic factors and PET parameters for PFS are shown in Table 3. The significantly longer mean PFS was observed in the low than high value group of the following individual parameters tumor size ($p = 0.008$), tumor status ($p = 0.009$), stage ($p = 0.013$), IV ($p = 0.012$), and SZV ($p = 0.015$). Other parameters did not predict the disease outcome. The subgroup analysis was also performed according to the type of histology. In the adenocarcinoma group, the significantly longer mean PFS was observed in the low than high value group of the following individual parameters: tumor status ($p < 0.001$), stage ($p < 0.001$), and IV ($p = 0.029$). Other parameters did not predict the disease outcome (Suppl. Table 8; see ESM). On the other hand, in the SCC group, the significantly longer mean PFS was observed in the low than high value group of the following individual parameters: tumor size ($p = 0.023$), lymph node status ($p = 0.003$), stage ($p = 0.008$), MTV ($p = 0.019$), TLG ($p = 0.027$), entropy ($p = 0.010$), and IV ($p = 0.019$). Other parameters did not predict the disease outcome (Suppl. Table 9; see ESM).

The results of Cox regression analyses are shown in Table 4. Tumor size, tumor status, stage, IV, and SZV were significant for PFS ($p = 0.014$, 0.003, 0.006, 0.017, and 0.022, respectively) at univariate analysis. At multivariate analysis, stage (HR 1.62, $p = 0.035$) and IV (HR 6.19, $p = 0.048$) remained significant and independent factors for PFS. The subgroup analysis was also performed according to the type of histology. Tumor status, stage, and IV were significant for PFS ($p = 0.039$, 0.041, and 0.048, respectively) at univariate analysis in the adenocarcinoma group. At multivariate analysis, IV (HR; 4.89, $p = 0.048$) remained significant and independent factors for PFS (Suppl. Table 10; see ESM). On the other hand, in the SCC group, lymph node status, stage, and IV were significant for PFS ($p = 0.020$, 0.007, and 0.037, respectively) at univariate analysis; however, these parameters were not significant at multivariate analysis (Suppl. Table 11; see ESM).

About the supplemental analyses for survival prediction in 87 patients, 29 patients showed eventually progression, and among them, 6 patients were died and 23 patients were alive. Median follow-up was 21.0 months (range, 1–71). The significantly longer mean PFS was observed in the low than high value group of the following clinicopathological parameters: tumor size ($p = 0.003$), tumor status ($p = 0.011$), lymph node status ($p = 0.013$), and stage ($p < 0.001$). Other SUV and volumetric parameters including $MTV_{42\ \%}$ and $TLG_{42\ \%}$ did not predict the disease outcome (Suppl Table 12; see ESM). On the Cox regression analyses, the same clinicopathological parameters (tumor size, tumor status, lymph node status, and stage) were significant for PFS ($p = 0.005$, 0.007, 0.006, and < 0.001, respectively) at univariate analysis. At multivariate analysis, only stage (HR 1.78, $p = 0.041$) remained as an independent factor for PFS (Suppl. Table 13; see ESM).

Figure 1 shows the risk differences in PFS among tumor status, stage, and between high and low IV and SZV groups, respectively. The representative images of non-progression and progression cases of [^{18}F]FDG-PET/CT image were shown in Figs. 2 and 3, respectively.

Table 3. Long-rank test of pathological and [^{18}F]FDG PET pretreatment parameters for progression-free survival in 55 NSCLC patients with $MTV_{2.5} > 10.0$ cm^3 received surgery

Parameter	Number	5-year survival proportion	Mean PFS[a] (mo)	*p* value
Age				0.14
≤ 69[b]	28	70.2 %	55 (44, 65)	
> 69[b]	27	41.2 %	42 (31, 54)	
Size (mm)				0.008
≤ 32[b]	31	55.1 %	51 (44, 59)	
> 32[b]	24	39.3 %	37 (25, 49)	
Histology				0.61
Adenocarcinoma	28	52.8 %	50 (39, 60)	
Squamous cell carcinoma	22	54.6 %	44 (34, 54)	
Others	5	40.0 %	36 (10, 36)	
Differentiation				0.64
Well differentiated	15	64.3 %	51 (37, 65)	
Moderately differentiated	28	57.8 %	43 (34, 53)	
Poorly differentiated	9	0 %	36 (17, 55)	
Undifferentiated	3	50.0 %	39 (6, 84)	
Tumor status				0.009
T1	17	90.0 %	58 (52, 64)	
T2	31	42.5 %	42 (32, 53)	
T3	5	53.3 %	41 (11, 72)	
T4	2	0 %	14 (5, 13)	
Lymph node status				0.29
N0	40	63.8 %	51 (43, 60)	
N1	7	0 %	39 (18, 60)	
N2	8	50.0 %	39 (17, 61)	
Stage				0.013
IA	13	88.9 %	58 (51, 64)	
IB	19	56.8 %	47 (33, 60)	
IIA	9	44.4 %	52 (37, 67)	
IIB	4	37.5 %	27 (2, 56)	
IIIA	9	37.0 %	34 (13, 55)	
IIIB	1	0 %	6 (6, 6)	
Post-operative adjuvant therapy				0.29
Not-performed	28	65.7 %	52 (42, 63)	
Performed	27	45.5 %	44 (32, 55)	
SUVmax				0.19
≤ 10.5[b]	28	56.7 %	53 (44, 63)	
> 10.5[b]	27	56.0 %	43 (31, 55)	
SUVmean				0.14
≤ 4.5[b]	28	64.5 %	54 (44, 65)	
> 4.5[b]	27	42.6 %	42 (30, 53)	
$MTV_{2.5}$ (cm^3)				0.10
≤ 14.6[b]	27	57.1 %	54 (45, 64)	
> 14.6[b]	28	51.0 %	42 (30, 54)	
$MTV_{42\ \%}$ (cm^3)				0.072
≤ 8.2[b]	28	60.7 %	54 (44, 64)	
> 8.2[b]	27	43.0 %	40 (28, 52)	
$TLG_{2.5}$				0.23
≤ 78.1[b]	28	51.5 %	52 (42, 62)	
> 78.1[b]	27	57.0 %	44 (32, 56)	
$TLG_{42\ \%}$				0.21
≤ 45.6[b]	28	49.5 %	52 (42, 62)	
> 45.6[b]	27	56.7 %	44 (31, 56)	
Entropy				0.079
≤ 7.16[b]	28	65.2 %	54 (44, 63)	
> 7.16[b]	27	45.4 %	41 (29, 54)	
Homogeneity				0.19
≤ 0.180[b]	27	53.6 %	52 (42, 63)	
> 0.180[b]	28	49.9 %	43 (31, 55)	
Dissimilarity				0.16
≤ 10.60[b]	28	48.3 %	42 (31, 54)	
> 10.60[b]	27	54.7 %	53 (42, 63)	
Intensity variability				0.012
≤ 7.30[b]	28	65.7 %	58 (49, 67)	
> 7.30[b]	27	43.6 %	36 (24, 47)	
Size-zone variability				0.015
≤ 164.5[b]	28	63.7 %	57 (48, 66)	
> 164.5[b]	27	44.5 %	39 (26, 51)	
Zone percentage				0.081
< 0.38[b]	27	49.7 %	37 (26, 47)	
≥ 0.38[b]	28	59.1 %	55 (45, 65)	

NCSLC, non-small cell lung cancer; PFS, progression-free survival; $MTV_{2.5}$, metabolic tumor volume (MTV) with SUVs ≥ 2.5; $MTV_{42\ \%}$, MTV with SUVs ≥ 42 % of SUVmax; $TLG_{2.5}$, total lesion glycolysis (TLG) with $MTV_{2.5}$; $TLG_{42\ \%}$, TLG with $MTV_{42\ \%}$

[a]Parentheses indicate 95 % confidence intervals

[b]Median values for age, tumor size and PET parameters

Discussion

Recurrence occurs even though a patient is in an early stage of NSCLC. For example, up to 20–30 % of patients with stage IA NSCLC recur after surgical treatment [8]. Therefore, it is essential to identify the prognostic factors that may predict these high-risk patients after surgical treatment and recommend individualized adjuvant therapy. In this context, we examined the values of [^{18}F]FDG-PET/CT image-based parameters related to primary tumor uptake including SUV, volumetric parameters, and heterogeneity texture parameters for prediction of prognosis of the surgically treated NSCLC patients.

SUV and Volumetric Parameters for Predicting Prognosis

On [^{18}F]FDG-PET/CT examinations, SUVmax is most commonly used to evaluate tumor response and recurrence because of high reproducibility and availability. However, it provides only the highest metabolic activity within the tumor, and it is not used to assess the entire tumor metabolic activity. For this reason, the usefulness of [^{18}F]FDG-volumetric parameters, such as MTV and TLG for predicting prognosis, has been investigated in patients with various types of cancer, and the prognostic value of these volumetric parameters for surgical patients with NSCLC was also examined, but the results were very diverse [22, 25–30]. Hyun, et al. [26] evaluated preoperative MTV and TLG calculated with mediastinal background SUVmean plus 2 standard deviations in patients with stages I and II NSCLC treated by surgery. At multivariate analyses, MTV and TLG were significantly associated with an increased risk of recurrence and death independently, but SUVmax was not a significant prognostic factor. Park et al. [22] examined the prognostic

Table 4. Univariate and multivariate Cox regression analyses for progression-free survival in 55 NSCLC patients with $MTV_{2.5} > 10.0$ cm^3 received surgery

Parameters	PFS			
	Univariate		Multivariate	
	Hazard ratio[a]	*p* value	Hazard ratio[a]	*p* value
Age	1.99 (0.78–5.05)	0.15		
Size	3.61 (1.29–10.07)	0.014	2.67 (0.78–9.14)	0.12
Histology	0.84 (0.34–2.07)	0.71		
Differentiation	1.24 (0.86–1.79)	0.25		
Tumor status	2.24 (1.33–3.79)	0.003	0.93 (0.42–2.05)	0.87
Lymph node status	1.52 (0.88–2.64)	0.13		
Stage	1.52 (1.13–2.05)	0.006	1.62 (1.03–2.53)	0.035
Post-operative adjuvant therapy	1.62 (0.65–4.05)	0.30		
SUVmax	1.82 (0.73–4.55)	0.20		
SUVmean	2.12 (0.79–5.09)	0.15		
$MTV_{2.5}$	2.13 (0.84–5.44)	0.11		
$MTV_{42\ \%}$	2.30 (0.90–5.87)	0.081		
$TLG_{2.5}$	1.73 (0.69–4.30)	0.24		
$TLG_{42\ \%}$	1.78 (0.71–4.46)	0.22		
Entropy,	2.26 (0.88–5.79)	0.088		
Homogeneity	0.54 (0.21–1.38)	0.20		
Dissimilarity	0.52 (0.20–1.33)	0.17		
Intensity variability	3.28 (1.23–8.72)	0.017	6.19 (1.02–37.61)	0.048
Size-zone variability	3.13 (1.18–8.29)	0.022	0.48 (0.08–2.90)	0.42
Zone percentage	2.18 (0.86–5.54)	0.10		

NSCLC, non-small cell lung cancer; PFS, progression-free survival; $MTV_{2.5}$, metabolic tumor volume (MTV) with SUVs ≥ 2.5; $MTV_{42\ \%}$, MTV with SUVs ≥ 42 % of SUVmax; $TLG_{2.5}$, total lesion glycolysis (TLG) with $MTV_{2.5}$; $TLG_{42\ \%}$, TLG with $MTV_{42\ \%}$
[a]Parentheses indicate 95 % confidence intervals

values of preoperative MTV and TLG calculated with the SUV threshold of 2.5 in addition to SUVmax in patients with surgically resected stage IA NSCLC. High TLG was shown to be an independent risk factor for overall survival (OS), but SUVmax and MTV were not significant prognostic factors. Conversely, Domachevsky et al. [27] showed both preoperative MTV and TLG calculated with the 42 % of SUVmax were not independent significant survival prognostic variables in patients with surgically resected stages I and II NSCLC.

In the present study, none of SUV and volumetric parameters was a significant prognostic factor, and the same results were obtained on the subgroup analysis according to the type of histology (adenocarcinoma and SCC). Furthermore, even in the supplemental analyses which were included 32 MTV ≤ 10.0 cm^3 patients, the same results were also obtained. The discrepancy in prognostic values of MTV and TLG among the studies may be partly attributed to different methods of tumor volume delineation. In fact, in our 87 study patients, there was some discrepancy in statistical significance for prediction of progression by MTV and TLG between the threshold criteria of SUV ≥ 2.5 and ≥ 42 % of SUVmax. A variety of isocontour threshold methods have been used to delineate tumor volume in [^{18}F]FDG-PET/CT [31]; however, the standard method to delineate tumor boundaries has not been defined [32]. In our study, the SUV threshold of 2.5 was adopted for tumor volume delineation according to the previous report [22, 28–30].

Texture Parameters for Predicting Prognosis

The ability of the [^{18}F]FDG PET texture parameters to predict the prognosis of NSCLC has been investigated [14–20]. Hatt et al. [15] examined whether the two local (entropy and dissimilarity) and two regional (high-intensity large-area emphasis [HILAE] and ZP) texture features were useful for predicting OS in 101 patients with clinical stage I-III NSCLC who received surgery, chemotherapy, or chemoradiotherapy, and entropy was identified as a significant predictor at multivariate analysis. Takeda et al. [20] examined the relationships of the four parameters (entropy, dissimilarity, HILAE, and ZP) with local control, PFS, and OS in 26 patients with stage I NSCLC treated with stereotactic body radiotherapy and reported that HILAE was a significant predictor for local control but not for PFS and OS.

To our knowledge, no study has examined the relationship between [^{18}F]FDG-texture parameters and prognosis of surgically treated NSCLC patients. In our study, tumor size, tumor status, stage, and regional parameters IV and SZV were significant for PFS at univariate analysis. At multivariate analysis, stage and IV were independent factors for PFS. IV, SZV, and ZP represent the regional tumor heterogeneity, such as variation of intensity between regions and in the size and alignment of homogeneous areas. IV and SZV measure the similarity of gray level values and zone sizes throughout the image, respectively.

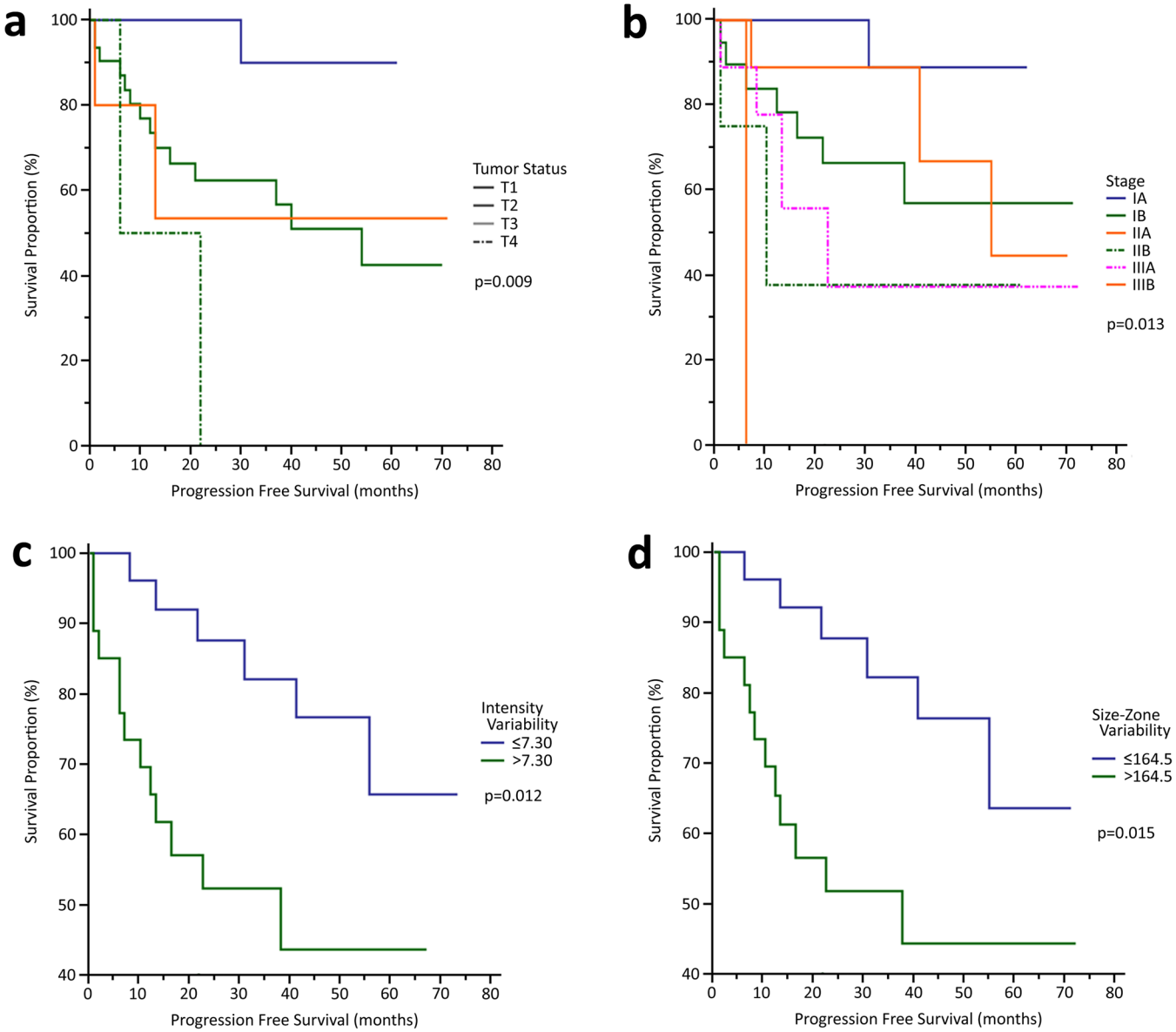

Fig. 1 Kaplan-Meier survival curves of the PFS in patients with NCSLC received surgery. **a** Tumor status, **b** stage, **c** IV, and **d** SZV. The significant differences are demonstrated in individual parameters.

These parameters are small if the gray level values or zone size are alike throughout the images. ZP shows the homogeneity and distributions of zones of the image in a specific direction. Heterogeneous images are prone to have higher IV, higher SZV, or lower ZP. On the other hand, the entropy, homogeneity, and dissimilarity reflect the

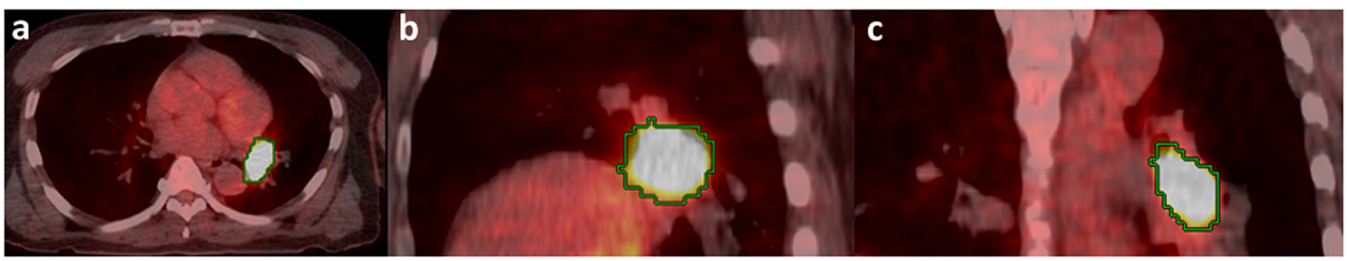

Fig. 2 [^{18}F]FDG-PET/CT: **a** transaxial, **b** coronal, and **c** sagittal images of a 67-year-old man with NCSLC (SCC, 35 mm, T3N0M0 stage IIB) without recurrence after operation. The green lines represent the borders of the VOI. The IV and SZV were 2.9 and 80.9, respectively. He was alive without progression 60 months after operation.

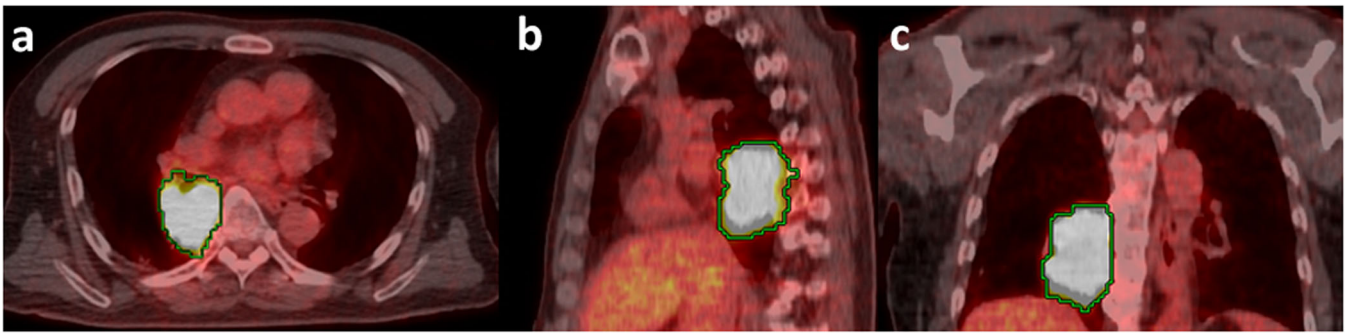

Fig. 3 [^{18}F]FDG-PET/CT: **a** transaxial, **b** coronal, and **c** sagittal images of a 66-year-old man with NCSLC (SCC, 60 mm, T4N0M0 stage IIIA) with progression after operation. The green lines represent the borders of the VOI. The IV and SZV were 45.1 and 695.3, respectively. He exhibited progression with local recurrence 12 months after operation.

relationships between pairs of voxel intensity and can be calculated using co-occurrence matrices, corresponding to the characterization of local heterogeneity [13, 33]. In our results, regional heterogeneity IV and SZV showed significant differences between progression and non-progression patients. Thus, we speculate that tumor progression would be more related with regional (macroscopic) than local (microscopic) heterogeneity, although the exact mechanisms for the results remain to be elucidated.

The regional heterogeneity parameters have the potential to provide additional value in addition to usual clinical data (stage) to decide the therapeutic strategy, such as neoadjuvant or adjuvant chemotherapy, determine the follow-up protocol, or predict tumor prognosis of surgically treated NSCLC patients. Such a tendency was also noted in surgically treated colorectal cancer patients [34].

Furthermore, we also performed the subgroup analysis to examine the difference in the prognostic role of pre-treatment [^{18}F]FDG-PET textural features in adenocarcinoma and SCC, respectively. Tumor status, stage, and IV were significant for PFS at univariate analysis and IV remained a significant factor for PFS at multivariate analysis in the adenocarcinoma group. On the other hand, lymph node status, stage, and IV were significant for PFS at univariate analysis in the SCC group; however, these parameters were not significant at multivariate analysis. These findings suggest that the regional heterogeneity texture feature IV may be more useful in cases of adenocarcinoma than SCC to predict PFS.

The study limitations were as follows: The texture heterogeneity features can be confounded by tumor volume effects in small volume tumors, especially those ≤ 10 cm^3 [15]. We only studied [^{18}F]FDG-avid NCSLCs with MTV > 10.0 cm^3, which resulted in a small study population. Thus, the obtained results of texture features are limited to relatively large NCSLCs, for example, larger than about 2.7 cm in spherical MTV diameter. The partial volume effect was not corrected. This effect becomes important when the tumor size is smaller than three times the FWHM of the PET scanner [35]. In our study, this effect might not significantly affect our results, because the smallest tumor size was about 2.7 cm in spherical MTV diameter, which was larger than three times the FWHM of the PET scanner (5.1 mm).

Conclusion

The regional heterogeneity texture features IV and SZV can predict tumor progression, and IV has the potential to predict prognosis of surgically treated NSCLC patients.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
This article does not contain any studies with animals performed by any of the authors.

Informed Consent

Informed consent was waived by the institutional review board for this retrospective study.

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