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Pretreatment ^{18}F-fluorodeoxyglucose Uptake in the Lung Parenchyma Predicts Poor Survival After Stereotactic Body Radiation Therapy in Patients With Stage I Non-Small Cell Lung Cancer

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Abstract

Purpose: In this study, we aimed to evaluate the prognostic value of fluorodeoxyglucose uptake in the lung parenchyma and the presence of subclinical interstitial lung disease on computed tomography as predictive factors for survival following stereotactic body radiation therapy in patients with stage I non-small cell lung cancer. **Methods:** We retrospectively evaluated 125 patients with stage I non-small cell lung cancer who underwent stereotactic body radiation therapy at our institute between December 2005 and March 2013 for various demographic and clinical parameters. The fluorodeoxyglucose uptake in the lung parenchyma corrected with computed tomography value (tissue fraction-corrected standardized uptake value) was quantified using fluorodeoxyglucose-positron emission tomography/computed tomography before the therapy. Additionally, the radiological findings of interstitial lung disease on computed tomography were evaluated. The prognostic analyses were performed using the Kaplan-Meier analysis and Cox proportional hazards regression model for univariate and multivariate analyses. **Results:** The median follow-up period was 39 months. The 3-year overall survival rate was 67.9%, and the 3-year progression-free survival rate was 52.0%. The multivariate analysis indicated that the tissue fraction-corrected standardized uptake value was correlated with the patients' overall survival ($P = .027$, hazard ratio: 2.694, 95% confidence interval: 1.109-8.057). The presence of subclinical interstitial lung disease showed no correlation with the overall survival ($P = .535$, hazard ratio: 1.256, 95% confidence interval: 0.592-2.473). **Conclusion:** The results indicated that fluorodeoxyglucose uptake in the lung parenchyma, expressed as the tissue fraction-corrected standardized uptake value, was an independent prognostic factor in patients with stage I non-small cell lung cancer who have received stereotactic body radiation therapy.

Keywords

FDG uptake, lung cancer, lung parenchyma, PET/CT, SBRT

Abbreviations

CT, computed tomography; CI, confidence interval; CRP, C-reactive protein; (^{18}F)-FDG, fluorodeoxyglucose; HR, hazard ratio; HRCT, high-resolution computed tomography; ICC, interclass correlation coefficient; ILD, interstitial lung disease; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PET, positron emission tomography; PFS,

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progression-free survival; PVE, partial volume effect; SBRT, stereotactic body radiation therapy; SUV_{max}, maximum of standardized uptake value; SUV_{mean}, mean of standardized uptake value of lung parenchyma without tissue fraction correction; SUV_{TF}, standardized uptake value of lung parenchyma with tissue fraction correction; TF, tissue fraction; VOIs, volumes of interest.

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Introduction

Stereotactic body radiation therapy (SBRT) is widely accepted as a standard treatment for patients with stage I non-small cell lung cancer (NSCLC) who are not eligible for surgery. Stereotactic body radiation therapy is minimally invasive; however, it has several contraindications, for example, since interstitial lung disease (ILD) is sometimes exacerbated by radiotherapy,[1] the Japan Clinical Oncology Group 0403 study indicates that severe interstitial pneumonitis or pulmonary fibrosis is one of the relative contraindications for SBRT in the treatment of patients with lung cancer. At our institution, we typically consider patients with subclinical ILD, that is, for whom oxygen therapy is not required, as eligible for SBRT after obtaining informed consent concerning the risk(s) of exacerbation/radiation pneumonitis. Severe radiation pneumonitis is reported in patients with subclinical ILD prior to SBRT for lung cancer,[2,3] and subclinical ILD is considered a significant risk factor for severe radiation pneumonitis.[4,5] Nevertheless, the impact of subclinical ILD on the prognoses of patients with NSCLC who have received SBRT has not been previously reported. Moreover, while subclinical lung disease can be detected with high-resolution computed tomography (HRCT),[6,7] a method to quantify the severity of subclinical ILD is yet to be established. Morphological assessment with HRCT is inadequate due to minimal abnormal computed tomography (CT) findings in patients with subclinical ILD.

Several recent studies have suggested that the regional accumulation of fluorodeoxyglucose (FDG) in the lung parenchyma is associated with inflammatory activity in the lung parenchyma[8]; hence, the severity of subclinical ILD cases that show no detectable morphological features on CT images could be quantitatively assessed by the FDG uptake in the lung parenchyma.[9-11]

We hypothesize that the uptake of FDG in the lung parenchyma is a prognostic factor in patients who have received SBRT for lung cancer. In this study, we aimed to evaluate the FDG uptake in the lung parenchyma, and the presence of subclinical ILD on HRCT as predictive factors for the patient outcome after SBRT for stage I NSCLC.

Materials and Methods

This was a single-institutional retrospective study. The study was conducted in accordance with the World Medical Association Declaration of Helsinki. The Institutional Review Board, Kofu Neurosurgical Hospital approved the study (on March 29, 2015) and waived the requirement for written informed consent from the patients.

Between December 2005 and March 2013, a total of 230 patients with primary NSCLC at clinical stage I (T1-T2aN0M0) underwent SBRT at our institution. Patients were excluded from the study if they did not undergo FDG-positron emission tomography (PET) prior to treatment (n = 58), did not undergo HRCT (n = 27), and were difficult to diagnose for recurrence due to development of another primary lung cancer after SBRT (n = 1). Patients were also excluded if they were not followed up after SBRT at our institution (n = 19). In total, 125 patients with stage I NSCLC who underwent SBRT were included (Table 1). The histological diagnosis of lung cancer was obtained in 107 tumors via transbronchial or CT-guided biopsies. The remaining 18 tumors were diagnosed as NSCLC by consensus among the 2 chest radiologists with 24 and 20 years of experience, respectively, based on the findings of HRCT, the clinical course of the disease over several follow-up CT examinations, and/or increased tracer radioactivity associated with enhanced FDG uptake on PET/CT scans.

The rationale for choosing SBRT as a treatment for stage I NSCLC in patients with comorbidities were contraindications for surgery or patients' preference for SBRT over surgery. The other eligibility criteria for SBRT included the performance status of ≤ 2 according to the World Health Organization guidelines.[12] The clinical stage was determined at our institutions' lung cancer board meeting by consensus among the chest radiologists, radiation oncologists, pulmonologists, and thoracic surgeons based on the findings of contrast-enhanced thoracic/abdominal CT scans, FDG-PET/CT scans, and brain magnetic resonance imaging (MRI).

The follow-up period was defined as the number of months from SBRT to death or censoring. The mean and median follow-up periods were 41 and 39 months (range, 8-103 months), respectively.

FDG-PET/CT was performed within 8 weeks (median 4, range 1-8) prior to the SBRT (Biograph Duo LSO; Siemens Medical Solutions, Erlangen, Germany). All patients were fasted for 6 hours. At 1 hour postinjection with ^{18}F-FDG (3 MBq/kg), they underwent a CT scan for attenuation correction (110 kV; 40-50 mA; tube rotation time, 0.8 second per rotation; pitch, 2; transverse field of view, 50 cm; and section thickness, 2.5 mm) followed by a PET scan from the neck to the thigh. The patients were instructed to maintain shallow breathing in a supine position during the scan. The visualization of the radioactive tracer was carried out in 3D mode (2 minutes per bed position). Transaxial emission images were reconstructed using

Table 1. Distribution of the Patients' Characteristics.

Characteristic	All patients (N = 125)
Age, years, mean (range)	78.52 (58-89)
Sex	
Male	67 (53.6%)
Female	58 (46.4%)
Brinkman index, mean (range)	687 (0-3360)
BED_{10}, median (range)	105.6 (75-150)
Histology	
Adenocarcinoma	63 (59.4%)
Squamous cell carcinoma	37 (29.6%)
NSCLC	
Nonspecified	7 (5.6%)
Unknown	18 (14.4%)
Tumor location	
Central	45 (36%)
Peripheral	77 (61.6%)
Tumor size, mm, median (range)	25 (11-50)
ILD +/−	26 (20.8%)/99 (79.2%)
Tumor SUV_{max}, median (range)	5.47 (0.48-27.47)
SUV_{mean}, median (range)	0.6 (0.25-0.8)
SUV_{TF}, median (range)	2.45 (1.53-3.55)
Pretreatment WBC count, /μL, <8000/≥8000	8 (6.4%)/109 (87.2%)
Not evaluated	8 (6.4%)
Pretreatment CRP, mg/dL, <0.3/≥0.3	29 (23.2%)/85 (68%)
Not evaluated	11 (8.8%)
Pretreatment LDH, U/L, <240/≥240	21 (16.8%)/95 (76%)
Not evaluated	9 (7.2%)
Pretreatment KL-6, U/mL, <500/≥500	80 (64%)/15 (12%)
Not evaluated	30 (24%)
Pretreatment FEV1 (%) <70%/≥70%	32 (25.6%)/58 (46.4%)
Not evaluated	35 (28%)

Abbreviations: BED_{10}, biologically effective dose (10 Gy); CRP, C-reactive protein; FEV1, forced expiratory volume (1.0 second); ILD, interstitial lung disease; KL-6, sialylated carbohydrate antigen 6; LDH, lactate dehydrogenase; NSCLC, non-small cell lung cancer; SUV_{max}, maximum of standardized uptake value; SUV_{mean}, mean of standardized uptake value of lung parenchyma without tissue fraction correction; SUV_{TF}, standardized uptake value of lung parenchyma with tissue fraction correction; WBC, white blood cell count.

the ordered subset expectation maximization method with 4 iterations and 28 subsets. The CT data were resized, from a 512 × 512 to a 128 × 128 matrix, to match the PET data to construct CT-based transmission maps for an attenuation correction of the PET data. The CT images were displayed on the monitor without changing the matrix size for reference and Hounsfield unit (HU) measurements.

Chest CT scans were performed using the following multidetector CT scanners: Aquilion 16 or Aquilion CX (Toshiba Medical Systems, Tokyo, Japan) or Light Speed or HiSpeed DXi (GE Healthcare, Milwaukee, Wisconsin). The detailed scanning parameters were detector collimation, 0.5 to 1.25 mm; beam pitch, 0.516 to 1.2; reconstruction increment, 1.0 mm; rotation time, 0.5 seconds; tube voltage, 120 kVp; and matrix, 512 × 512. The tube currents were determined by the machine's automatic exposure control (actual range, 110-400 mA). CT scans were obtained in the supine position at full inspiration. The HRCT images were reconstructed with slice thickness of 1.0 to 1.25 mm and field of view of 14.5 to 25.0 cm.

The PET/CT images were reviewed by a nuclear medicine physician with 12 years of experience, who was blinded to the patient outcome, using a dedicated image workstation (e-soft-PET; Siemens Medical Solutions, Erlangen, Germany). Elliptical volumes of interest (VOIs) with sizes of around 20 cm^3 (12.1-21.4 cm^3) were semiautomatically placed on the apex of bilateral upper lobes, right middle lobe, lingular segment of the left upper lobe, and the dorsal lower regions of bilateral lower lobes with reference to the 3 imaging planes (axial, sagittal, and coronal PET/CT images) to avoid the region affected by the primary lung cancer and the artifacts related to diaphragm motion. These VOIs were used to measure the mean HU values (HU_{mean}) on low-dose CT acquired with the PET and the mean standardized uptake values (SUV_{mean}) on PET.

Variation in the tissue HU can affect the acquisition of the tracer uptake in lung PET.[13] To compensate for this effect, the tissue fraction (TF) correction method was applied.[14] The standardized uptake value of lung parenchyma with TF correction (SUV_{TF}) measurement represents the underlying metabolic characteristics of the tissue regardless of the variations in the background air of the target region. The TF factor (κ) and SUV_{TF} were defined by the following formulae:[15]

$$\kappa = (HU_{lung} - HU_{air})/(HU_{tissue} - HU_{air})$$

$$SUV_{TF} = SUV_{mean}/\kappa,$$

where HU_{tissue} and HU_{air} are the CT values of the pectoralis major muscle with the largest spherical VOI not exceeding the muscle and air, respectively. The SUV_{TF} measurements were averaged with the 6 VOIs to represent the mean of corrected FDG uptake in the whole lung parenchyma. In other words, SUV_{TF} represented the true FDG uptake in the whole lung except for the primary tumor. The maximum of standardized uptake value (SUV_{max}) of the primary tumor was also obtained. We used data from a nuclear medicine physician with 12 years of experience who was a main observer to calculate SUV_{TF}. In addition, SUV_{max} of the primary tumor was also evaluated.

For assessment of the interobserver agreement in SUV_{TF} measurements, another radiologist with 5 years of experience in PET imaging also placed the VOIs.

For lung CT analysis, the patients were classified into 2 groups, that is, with or without subclinical ILD, by a chest radiologist with 20 years of experience using HRCT. During the evaluation, any of the following CT criteria[16] were required for the diagnosis of subclinical ILD: (1) presence of independent ground-glass abnormalities, (2) reticular abnormalities, (3) traction bronchiectasis, (4) nonemphysematous cyst, (5) honeycombing, and no treatment required for the lung disease, that is, typically asymptomatic patients.

The SBRT eligibility criteria are described above. There were no restrictions based on the location of eligible tumors, irrespective of whether located adjacent to a major bronchus, blood vessel, the chest wall, or the esophagus. Stereotactic

body radiation therapy was performed with noncoplanar dynamic arcs or multiple static ports using a unit that included a linear accelerator (EXL-15DP; Mitsubishi Electric, Tokyo, Japan) coupled to and sharing a common couch with a CT scanner (HiSpeed DX/I; GE Yokogawa Medical Systems, Tokyo, Japan). The isocenter was adjusted using image guidance with a CT-on-rail system in all fractions.[16] A total dose of 48 to 70 Gy (median 48), calculated using Clarkson's algorithm, was administered in 4 to 10 fractions at the isocenter.

The patients were followed up every 3 months after SBRT at the outpatient clinic. At each follow-up visit, the tumor markers and non-contrast-enhanced CT measurements were obtained. Posttreatment PET was performed in cases with abnormal findings on CT or tumor markers. Levels of tumor markers such as carcinoembryonic antigen, squamous cell carcinoma, and cytokeratin-19 fragment were used as a reference for recurrence but not to confirm a diagnosis.

The diagnosis of recurrence was based on the histopathology findings or findings on serial imaging including CT images, MRI, or PET/CT images that suggested the progression of lesions over the 6-month follow-up period. Cancer development in other organs during the follow-up was also recorded. According to the findings, until the last follow-up, all patients were categorized into the following groups: dead, alive with recurrence, and alive without recurrence. Overall survival (OS) and progression-free survival were defined as the number of months from SBRT to dead and recurrence, respectively. The number of months from SBRT to the last follow-up was used for censored cases. In addition, radiation-induced pneumonitis was evaluated using the Common Terminology Criteria for Adverse Events ver. 4.0.

Besides subclinical ILD and PET/CT parameters, the following clinical variables were evaluated: age; sex; Brinkman index (the number of cigarettes smoked per day multiplied by the number of years of smoking); T stage; histopathology (adenocarcinoma or other); tumor location (central or peripheral); the biologically effective dose of 10 Gy; SUV_{max} of the primary tumor; blood work and physiological data, including white blood cell count; C-reactive protein (CRP) concentrations; lactate dehydrogenase concentrations; concentration of sialylated carbohydrate antigen 6; and the percentage of forced expiratory volume in 1 second. Central tumor location was defined as within 2 cm of the proximal bronchial tree, heart, great vessels, trachea, or other mediastinal structures[17]; all other tumors were categorized as peripheral. The OS and PFS rates were evaluated using the Kaplan-Meier method using a log rank test. The Youden index in the receiver–operating characteristic curve analysis was used to identify optimal cutoff values for binarization of tumor SUV_{max}, SUV_{mean}, and SUV_{TF} as continuous variables. The prognostic values of the variables were assessed using a Cox proportional hazards regression model in both univariate and multivariate analyses. Based on the univariate analysis, only variables with a P value of $<.10$ were included in the multivariate analysis.

The degree of interobserver agreement was assessed by interclass correlation coefficient (ICC).

Results

Table 1 shows the patient characteristics. All patients underwent SBRT without complications or interruptions. The OS and PFS rates at 3 years were 67.9% and 52.0%, respectively. During the follow-up period, recurrence was observed in 53 patients; the total numbers of local/regional lymph node recurrences and distant metastases were 29, 23, and 36, respectively. The median SUV_{mean} and SUV_{TF} were 0.6 (range, 0.25-0.8) and 2.45 (range, 1.53-3.55), respectively. The morphological assessment of the HRCT showed that 26 cases had interstitial abnormalities in the lung parenchyma, of which 13 had independent ground-glass abnormalities, 10 had reticular abnormalities, 3 had traction bronchiectasis, and 99 had no interstitial abnormalities.

Radiation-induced pneumonitis was observed in 4 patients with grade 3 and 1 patient with grade 2. Corticosteroid therapy was required in 3 patients. Of the 5 patients with radiation-induced pneumonitis, 2 had subclinical ILD and 3 had lung SUV_{TF} of $\geq$2.28. We could not find any relationship between radiation-induced pneumonitis and the presence of subclinical ILD or SUV_{TF}. There were also no correlations between SUV_{TF} and the subclinical ILD, or SUV_{TF} and mean HU_{lung} (correlation coefficient = 0.014, 0.289) or mean HU_{lung}.

Kaplan-Meier analysis indicated that the OS of patients with subclinical ILD (median OS [95% confidence interval (CI)] of 31 [26-41] months) was significantly lower than of those without subclinical ILD (56 [43-73] months) ($P = .0108$, Figure 1A). The OS curves were also well stratified with SUV_{TF} using a cutoff value of 2.28, and the OS of patients with high SUV_{TF} (38 [22-43] months) was also significantly lower than those with low (65 [21-103] months) SUV_{TF} ($P = .0177$, Figure 1B). For PFS, no significant difference was observed between patients with (22 [14-65] months) and without (42 [28-48] months) subclinical ILD ($P = .1261$) or with high (38 [22-43] months) and low (65 [21-103] months) SUV_{TF} ($P = .0678$) (Figure 2A and B).

Based on univariate analyses, the factors affecting OS included male sex (hazard ratio [HR] [95% CI] of 2.362 [1.357-4.371]; $P = .002$), presence of subclinical ILD (HR, 2.001 [1.128-3.397]; $P = .019$), tumor SUV_{max} of $\geq$ 3.99 (HR, 2.002 [1.230-3.34]; $P = .005$), lung SUV_{TF} of $\geq$ 2.28 (HR, 2.005 [1.152-3.960]; $P = .014$), and a CRP concentration of $\geq$ 0.3 mg/dL (HR, 1.793 [1.031-3.031]; $P = .039$). Factors affecting the PFS included T stage (HR, 1.789 [1.117-2.802]; $P = .016$), central tumor location (HR, 1.71 [1.101-2.643]; $P = .017$), and tumor SUV_{max} of $\geq$ 3.99 (HR, 1.828 [1.179-2.871]; $P = .007$) (Table 2).

The multivariate analyses revealed that the following factors were correlated with OS: lung SUV_{TF} of $\geq$2.28 (HR, 2.694 [1.109-8.057]; $P = .027$) and T stage (HR, 2.421 [1.2-4.704]; $P = .015$). The tumor SUV_{max} of $\geq$3.99 (HR, 1.704 [1.09-2.7]; $P = .019$) and central tumor location (HR, 1.592 [1.016-2.483]; $P = .042$) were correlated with PFS (Table 3).

The interobserver agreement in SUV_{TF} measurements was excellent (ICC, 0.955). ICC for the SUV_{max} of the primary

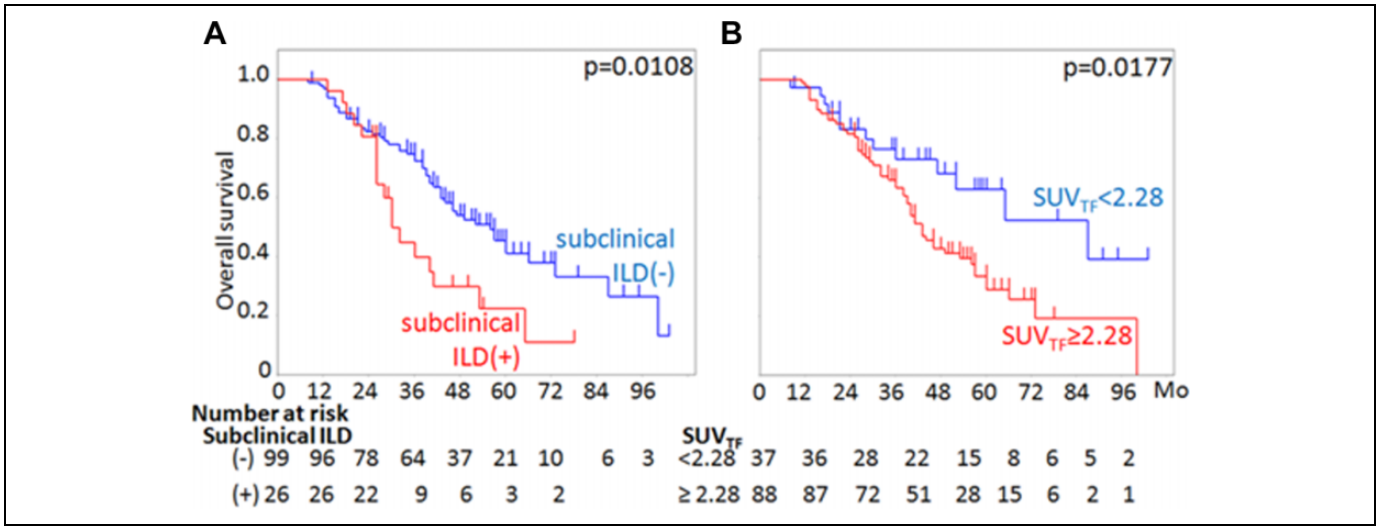

Figure 1. Kaplan-Meier survival curves for overall survival of patients with stage I non-small cell lung cancer. A, stratified by subclinical ILD (+) (in red) versus (−) (in blue). B, Stratified by high SUV_{TF} (≥2.28) (in red) versus low SUV_{TF} (<2.28) (in blue). ILD, interstitial lung disease; SUV_{TF}, tissue fraction-corrected standardized uptake value.

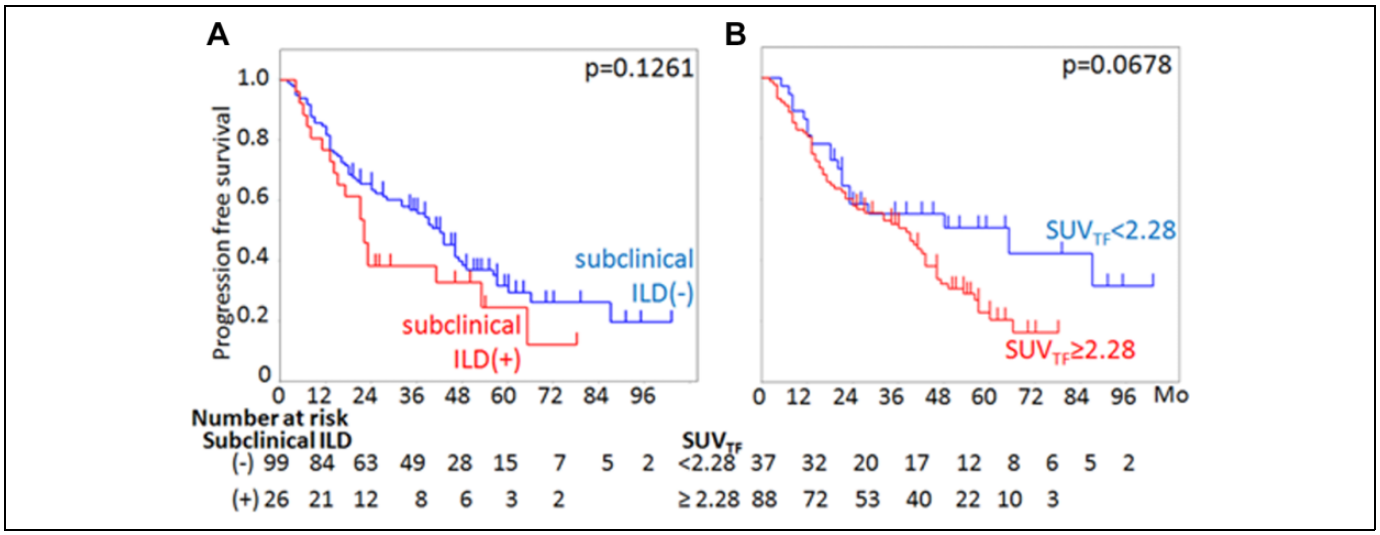

Figure 2. Kaplan-Meier survival curves for progression-free survival of patients with stage I non-small cell lung cancer. A, Stratified by subclinical ILD (+) (in red) versus (−) (in blue). B, Stratified by high SUV_{TF} (≥2.28) (in red) versus low SUV_{TF} (<2.28) (in blue). ILD, interstitial lung disease; SUV_{TF}, tissue fraction-corrected standardized uptake value.

tumor was not assessed because it was a reproducible value for solitary pulmonary nodules. In Figure 3, 4 representative cases are shown.

Discussion

Our results suggested that SUV_{TF}, which represents the pretreatment FDG uptake in the lung parenchyma, was correlated with OS in patients who underwent SBRT for stage I lung cancer. Conversely, the presence of subclinical ILD based on morphological changes detected on HRCT of the lungs was unrelated to the prognosis after SBRT.

Previous reports indicated that subclinical ILD or interstitial lung abnormalities were significant risk factors for the development of radiation pneumonitis in patients with lung cancer who were to undergo SBRT.[2,3] In our series, 5 patients experienced radiation pneumonitis with grade 3 (4 patients) or 2 (1 patient); among these, 3 patients were without subclinical ILD. However, the occurrence of radiation pneumonitis showed no statistical relationship with the OS.

The FDG uptake and SUV are overestimated in the posterior lung parenchyma due to the gravity-dependent congestion, which leads to an unexpected number of erythrocytes (more actual FDG uptake) and increased parenchymal attenuation on CT (overestimates of the FDG uptake value on PET/CT).[18] As

Table 2. Univariate Analysis of Predictors of OS and PFS in Patients Treated With SBRT for Stage I Non-Small Cell Lung Cancer.

	OS		PFS	
Characteristics	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (continuous)	1.204 (0.909-1.067)	.214	1.027 (0.992-1.067)	.13
Gender (male vs female)	2.362 (1.357-4.371)	.002[a]	1.249 (0.784-2.053)	.356
T stage (T2a vs T1)	1.578 (1.357-4.371)	.08	1.789 (1.117-2.802)	.016[a]
Histology (adeno vs other)	0.86 (0.533-1.381)	.532	0.999 (0.646-1.544)	.997
Location (central vs peripheral)	1.487 (0.915-2.401)	.108	1.71 (1.101-2.643)	.017[a]
BED_{10} (continuous)	0.993 (0.972-1.013)	.487	0.9996 (0.98-1.018)	.969
Brinkman index^{-3} (continuous)	1.232 (0.930-1.570)	.139	1.011 (0.756-1.303)	.937
Subclinical ILD (+ vs −)	2.001 (1.128-3.397)	.019[a]	1.487 (0.864-2.443)	.146
Tumor SUV_{max} (continuous)	1.039 (0.993-1.081)	.096	1.041 (0.988-1.079)	.06
Tumor SUV_{max} (≥3.99 vs <3.99)	2.002 (1.230-3.34)	.005[a]	1.828 (1.179-2.871)	.007[a]
SUV_{mean} (continuous)	1.673 (0.231-11.811)	.608	1.635 (0.277-9.447)	.585
SUV_{mean} (≥0.375 vs <0.375)	0.612 (0.345-1.172)	.132	0.661 (0.383-1.226)	.179
SUV_{TF} (continuous)	1.996 (0.98-4.082)	.057	1.2 (0.643-2.238)	.567
SUV_{TF} (≥2.28 vs <2.28)	2.005 (1.152-3.960)	.014[a]	1.617 (0.977-2.816)	.062
WBC ≥ 8000 (≥8000 vs <8000)	1.011 (0.352-2.295)	.981	0.824 (0.289-1.848)	.668
CRP ≥ 0.3 (≥0.3 vs <0.3)	1.793 (1.031-3.031)	.039[a]	1.37 (0.807-2.245)	.236
LDH ≥ 240 (≥240 vs <240)	1.023 (0.489-1.931)	.948	1.138 (0.598-2.006)	.677
KL-6 ≥ 500 (≥500 vs <500)	1.302 (0.588-2.573)	.491	1.368 (0.653-2.585)	.384
FEV1 < 70% (<70% vs ≥70%)	1.747 (0.963-3.147)	.066	1.31 (0.751-2.245)	.336

Abbreviations: adeno, adenocarcinoma; BED_{10}, biologically effective dose (10 Gy); CRP, C-reactive protein; FEV1, forced expiratory volume (1.0 second); HR, hazard ratio; ILD, interstitial lung disease; KL-6, sialylated carbohydrate antigen 6; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiation therapy; SUV_{max}, maximum of standardized uptake value; SUV_{mean}, mean of standardized uptake value of lung parenchyma without tissue fraction correction; SUV_{TF}, standardized uptake value of lung parenchyma with tissue fraction correction; WBC, white blood cell count.
[a]Statistically significant.

Table 3. Multivariate Analysis of Predictors of OS and PFS in Patients Treated With SBRT for Stage I Non-Small Cell Lung Cancer.

	OS		PFS	
Characteristics	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender (male vs female)	1.594 (0.721-3.784)	.255		
T stage (T2a vs T1)	2.421 (1.2-4.704)	.015[a]	1.528 (0.945-2.42)	.083
Location (central vs peripheral)			1.592 (1.016-2.483)	.042[a]
Subclinical ILD (+ vs −)	1.256 (0.592-2.473)	.535		
Tumor SUV_{max} (≥3.99 vs <3.99)	1.56 (0.801-3.088)	.191	1.704 (1.09-2.7)	.019[a]
SUV_{TF} (≥2.28 vs <2.28)	2.694 (1.109-8.057)	.027[a]	1.4 (0.836-2.463)	.206
CRP (≥0.3 vs <0.3)	1.029 (0.489-2.095)	.938		
FEV1 (<70% vs ≥70%)	1.239 (0.607-2.529)	.554		

Abbreviations: CRP, C-reactive protein; FEV1, forced expiratory volume (1.0 second); HR, hazard ratio; ILD, interstitial lung disease; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiation therapy; SUV_{max}, maximum of standardized uptake value; SUV_{TF}, standardized uptake value of lung parenchyma with tissue fraction correction; SBRT, stereotactic body radiation therapy.
[a]Statistically significant.

patients are examined in a supine position, the measurement of FDG uptake cannot represent the active inflammation alone. To deal with this problem, we applied TF-based correction,[13,14] which is known to correct the apparent SUV in the area showing higher attenuation in the lungs (Figure 3C).

Then, in our study, some cases, which seemed to have uptakes in the posterior lung parenchyma, were revealed not to have accumulation by the TF correction.

Our results have some implications for patient care. As ILD is a risk factor for radiation pneumonitis, the prognosis of patients with subclinical ILD would be poorer than those without subclinical ILD assessed by HRCT. Based on our results, the prognosis after SBRT is more precisely indicated by the FDG-PET parameter (SUV_{TF}) than by the HRCT findings (subclinical ILD). Combined with the previous reports,[19,20] FDG-PET could facilitate the evaluation of the vulnerability of the lung parenchyma to irradiation. Although we cannot explain the exact cause of the low OS in patients with high lung SUV_{TF}, FDG-PET is more useful than HRCT to identify patients with underlying lung disease.

In addition, high SUV_{max} of the primary tumor was correlated with PFS but not with OS in the current study. In

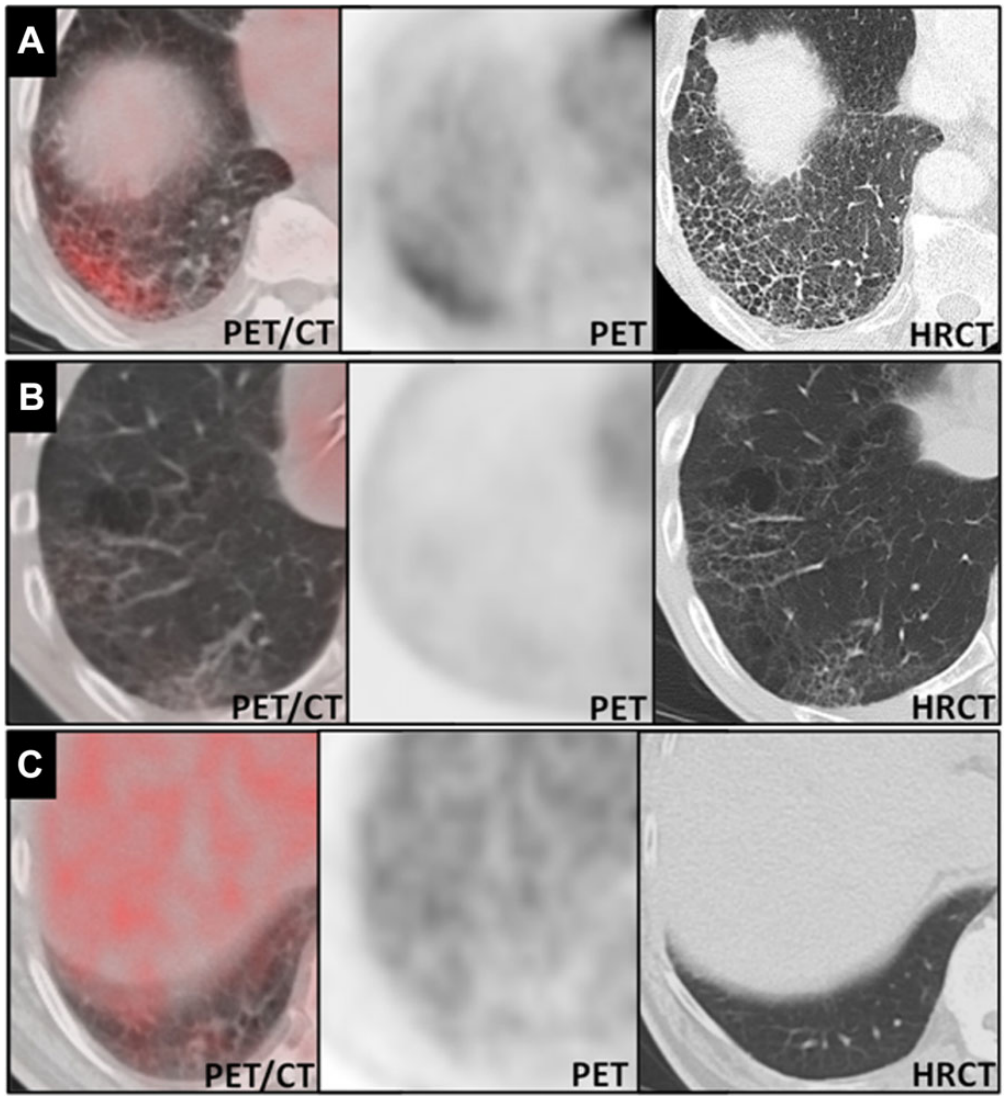

Figure 3. Positron emission tomography/computed tomography (CT) and CT images from patients with stage I non-small cell lung cancer before stereotactic body radiation therapy. A, A 79-year-old man with interstitial lung disease (ILD) on CT with focal fluorodeoxyglucose (FDG) uptake; the standardized uptake value of lung parenchyma with tissue fraction correction (SUV_{TF}) of the lung parenchyma was high ($SUV_{TF} = 2.78$). The presence of active inflammation of the lung parenchyma was suspected. B, An 80-year-old man with ILD without apparent increase in FDG uptake. The SUV_{TF} of the lung parenchyma was low ($SUV_{TF} = 2.15$). The presence of active inflammation was not suspected. C, A 76-year-old man with the presence of increased density on CT with slightly elevated FDG uptake in the lower dorsal lung parenchyma. The SUV_{TF} value was low ($SUV_{TF} = 2.12$). Gravity-related, density-dependent changes were suspected.

agreement with our result, a recent meta-analysis indicated the prognostic significance of pretreatment SUV_{max} of the primary tumor in patients with early-stage NSCLC treated with SBRT.[21] Further prospective studies are needed to clarify this issue. Another study has reported SUV_{max} of the primary tumor in locally advanced patients with NSCLC who underwent curative conventional radiotherapy predicted the prognosis.[22] This difference between these reports might be caused by the partial volume effect (PVE) due to the limited special resolution of PET/CT. Partial volume effect can lead to quantitative underestimation of FDG uptake, especially in small tumors.[23]

Our study had several limitations. The primary limitations included the retrospective study design and small cohort. Second, the PET/CT scans were performed during breathing without a respiratory-gating system, which could have resulted in the inaccurate analysis of FDG uptake. Third, our study sample had a high local recurrence rate. Since we did not perform PET in patients who were unlikely to have metastatic disease (eg, patients with tumors in which ground-grass opacities predominated) at the beginning of the study, our study sample was biased. Fourth, the pulmonary inflammatory status itself could be related to the prognosis; a further trial with a control group is required to confirm whether the pulmonary inflammation itself

is related to a poor prognosis. Fifth, the dichotomized version of the variables for the multivariate analysis could have led to biased results; the use of the original continuous variable is preferable. Sixth, the PET/CT was acquired within 8 weeks before SBRT. Some findings of the lesions that had high potential for tumor growth might have been different at the time of the PET/CT and SBRT. Therefore, it might have affected the results. Seventh, it has been reported that the parameters of primary lesions considering tumor volume, such as total lesion glycolysis and metabolic tumor volume, were useful for predicting the prognosis.[22] However, we evaluated the tumor size by the T stage. It may also have some effects on the results.

Conclusion

The uptake of FDG in the lung parenchyma was correlated with OS in patients with stage I NSCLC who were treated with SBRT, that is, high SUV_{TF} during the pretreatment staging of FDG-PET predicted poor survival.

Declaration of Conflicting Interests

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