Predictive Value of Preoperative Volume-Based ^{18}F -2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography/Computed Tomography Parameters in Patients with Resectable Lung Adenocarcinoma

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Abstract

Purpose This study aimed to investigate the prognostic value of metabolic tumor volume (MTV) and total lesion glycolysis (TLG), which are volume-based PET parameters, using ^{18}F -2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) in patients with surgically resectable lung adenocarcinoma.

Methods We retrospectively evaluated 149 patients with lung adenocarcinoma who underwent ^{18}F -FDG PET/CT before surgical resection. Maximum standardized uptake value (SUVmax), MTV, and TLG of the primary tumor with threshold value of SUVmax 30, 40, and 50% were calculated, respectively. To compare the predictive performance of volume-based PET parameters, recurrence-free survival was assessed using the Kaplan-Meier method.

Results The study included 70 males and 79 females with an average age of 65.8 years. The median follow-up time was 45.4 months. Recurrence was observed in 53 patients (35.6%). The mean $\pm$ SD SUVmax, MTV_{30%}, and TLG_{30%} of the entire cohort were 4.79 ± 2.94 , 19.45 ± 24.85 , and 56.43 ± 101.88 , respectively. The cut-off values of MTV_{30%} and TLG_{30%} for recurrence were 11.07 and 30.56, respectively. The 1-year recurrence-free survival (RFS) rate was 96.5% in low-MTV_{30%} patients compared with 86.2% in high-MTV_{30%} patients ($p = 0.018$) and 96.0% in low-TLG_{30%} patients compared with 88.5% in high-TLG_{30%} patients ($p < 0.001$). On univariate and multivariate analysis, TLG_{30%} (HR, 2.828, $p < 0.001$; HR, 2.738, $p < 0.001$, respectively) was an independent prognostic factor for predicting recurrence-free survival (RFS).

Conclusion TLG_{30%} value was observed to be a significant prognostic factor for RFS in patients with lung adenocarcinoma treated by surgical resection.

Keywords Lung adenocarcinoma · FDG PET/CT · Recurrence · Metabolic tumor volume · Total lesion glycolysis

Introduction

Lung cancer is one of the most common cancers in both men and women and the most common cause of cancer-related death in the world [1, 2]. Non-small cell lung cancer (NSCLC) accounts for up to 85–90% of all lung cancer cases. Patients with stage I and II and selective stage III NSCLC are considered eligible for curative surgical resection with complete lymph node dissection. After complete surgical resection, however, a large number of patients experience recurrence (with a 5-year recurrence rate up to 39.6%) and die [3, 4]. Loco-regional recurrence and distant metastases are the most common causes of treatment failure [5, 6]. High TNM stage

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has been considered a poor prognostic factor in patients with NSCLC. Furthermore, considerable number of patient experience relapse after curative treatment despite low-stage disease status, and up to 25% of patients with stage I NSCLC experience relapse after surgical resection. Because patients with the same disease stage could have diverse tumor- and patient-specific prognostic factors, it is necessary to take into consideration these factors for determining the individual therapeutic strategy [7, 8].

^{18}F -2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) is one of the important imaging modalities for staging, determining treatment strategy, and predicting the prognosis of NSCLC. ^{18}F -FDG PET parameters such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) can provide useful data to understand tumor metabolic activity. ^{18}F -FDG PET parameters have been studied as potential prognostic factors. The SUVmax is the most commonly used FDG PET parameter because of its reproducibility and availability. SUVmax is the value of a single voxel with the highest radiotracer activity within the region of interest (ROI) of the tumor, whereas volume-based parameters MTV and TLG represent the metabolic tumor burden. There has been interest in the clinical significance of volume-based parameters for NSCLC. Studies have reported that MTV and TLG showed better performance for predicting the prognosis compared with SUVmax in high stage III and IV NSCLC [9, 10]. In patients with NSCLC treated by surgical resection, MTV and TLG showed better predictive performance compared with SUVmax for recurrence-free survival (RFS) and overall survival (OS). MTV_{2.5} (measured by using the lowest threshold value of SUV2.5) was reported as a significant prognostic factor for OS [11]. However, there were no significant difference in RFS among MTVs and TLGs that were calculated according to various thresholds of SUVs (2.5, 3.0, 3.5, 4.0). Furthermore, recent studies have shown that TLG was also a significant prognostic factor for predicting RFS and OS in early stage I NSCLC [12]. The most recent study reported the prognostic value of MTV in patients with stage I NSCLC treated by surgical resection [13].

NSCLC comprise several histologic subtypes, which include adenocarcinoma and squamous cell carcinoma. Studies have reported that SUVmax, MTV, and TLG were significantly lower in adenocarcinoma than in squamous cell carcinoma patients and adenocarcinoma had a worse prognostic outcome compared with squamous cell carcinoma based on the potential to metastasize [14, 15]. This finding may have an important influence on the interpretation of ^{18}F -FDG PET scans of patients with these two NSCLC subtypes. Based on the results of these previous studies on the metabolic characteristics of adenocarcinoma and other histologic subtypes and the prognostic value of volume-based PET parameters, we

hypothesized that volume-based PET parameters using lower threshold values can show better performance for predicting prognosis in lung adenocarcinoma patients.

The aim of this study is to investigate the prognostic value of volume-based PET parameters MTVs and TLGs using various threshold values (30, 40, and 50%) of SUVmax in patients with lung adenocarcinoma who underwent surgical resection and to ascertain the optimal threshold value to calculate the MTV and TLG to predict the recurrence.

Materials and Methods

Patients

This study was a retrospective review of lung cancer database at our hospital using data collected between January 2010 and December 2015. The inclusion criteria for this study required patients to have the following: (1) histologically proven lung adenocarcinoma, (2) a histopathologic confirmed mediastinal lymph node stage, and (3) treated with curative-intent surgical resection. Patients with stage I and II and selective stage III lung adenocarcinoma with diagnosis based in the 7th edition TNM classification after surgical resection and complete lymph node dissection were enrolled. Patients who met the following criteria were excluded: (1) any chemotherapeutic or radiotherapeutic treatments before the ^{18}F -FDG PET/CT scan, and (2) other pre- or coexisting primary malignancy. The study protocol for this retrospective study was reviewed and approved by institutional review board at our institution (2018AN0195).

Clinical Follow-up

We retrospectively reviewed the medical records, and pathologic data. Chest computed tomography (CT), ^{18}F -FDG PET/CT, and endobronchial ultrasound bronchoscopy were performed preoperatively. Surveillance of recurrence was performed primarily using imaging modalities. Postoperatively, chest CT scans were obtained at 3-month intervals and PET/CT scans were also obtained to detect recurrence. Recurrence was determined using primarily physician clinical assessment, radiographic reports, and/or review of imaging studies. For cases suspected to have recurrence, we additionally performed invasive procedures including CT-guided needle biopsy or bronchoscopic biopsy to support the clinical diagnosis. Local recurrence was defined as recurrence occurring on the resection margin or bronchial stumps. Regional recurrence was defined as recurrence occurring in the ipsilateral lung; mediastinal, hilar, and supraclavicular lymph nodes; or pleural cavity. Distant metastases were defined as lesions occurring in the contralateral lung, adrenal glands, brain, liver, bone, or other organs.

¹⁸F-FDG PET/CT Image

¹⁸F-FDG PET/CT was performed using Gemini TF (Philips Medical Systems, Cleveland, OH, USA). All patients fasted for 6 h and had serum glucose levels < 140 mg/day before the scan. CT scans were obtained followed by PET for 1 min/bed 1 h after an intravenous injection of 370–555 MBq ¹⁸F-FDG according to body weight. The PET unit had an 18-cm axial fields of view and 4.4-mm spatial resolution. A low-dose CT scan was obtained for attenuation correction and localization on a 16-slice multi-detector helical CT (120 kVp; 50 mA; 0.75-s rotation time; 0.75-mm slice collimation; 4-mm scan reconstruction, with a reconstruction index of 4 mm; 512 × 512 matrices). The PET data acquired from the thigh to head for 1.0 min per frame were reconstructed iteratively using a three-dimensional row action maximum likelihood algorithm (RAMLA) with low-dose CT data sets for correcting attenuation.

Measurement of PET Parameters

PET parameters were determined using a dedicated workstation (Extended Brilliance Workspace 4.0 with a PET/CT viewer for automated image registration, Philips, Amsterdam, The Netherlands). We reviewed all the available clinical information, and interpreted the PET/CT image. We measured the MTVs and TLGs of malignant lung lesions with semiautomatic method. After reviewing the margin and shape of the malignant lung lesion through chest CT image, we drew spherical shape of volume of interest (VOI) on PET scan image, which included over gross tumor volume on CT image. Within drawn VOI, the MTVs were automatically calculated using an isocontour method with variable threshold values. The SUVmax was defined as the voxel with the highest count

within the VOI. The MTV_{30%}, MTV_{40%}, and MTV_{50%} were defined as a volume greater than a fixed threshold of 30, 40, and 50% of the maximum intratumoral activity, respectively. Additionally, we measured the MTV and TLG with fixed threshold value, SUV2.0. Representative cases of measuring MTV_{30%} and TLG_{30%} are shown in Fig. 1. In Fig. 1a, a 3.1-cm lesion in right lower lung (T1b, stage IB) showed mild FDG uptake with SUVmax 2.3, MTV_{30%} 15.3, TLG_{30%} 17.9. In Fig. 1b, a 3.6-cm lesion in right upper lung (T2a, stage IIB) showed mild FDG uptake with SUVmax 2.6, MTV_{30%} 29.5, TLG_{30%} 37.0.

Previous studies reported that a higher lymph node ratio correlated with poor prognostic outcome in NSCLC. We calculated the lymph node ratio (LNR) as the ratio between the number of positive N1 and N2 lymph nodes and the number of lymph nodes removed among all mediastinal lymph nodes during the surgery. Based on the prior studies, patients were divided into two groups: low-LNR ≤ 0.15 and high-LNR > 0.15 [16, 17].

Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 software (SPSS INC., Chicago, IL, USA). All *p* values < 0.05 were considered significant. Clinical parameters were described as means ± standard deviations of the mean for continuous variables and as frequencies (%) for categorical variables. Student's *t* test or Mann-Whitney *U* test and χ^2 test or Fisher's exact tests were applied to compare the continuous and categorical variables, respectively.

The primary endpoint was RFS, which was measured from the date of the surgical operation to the date of recurrence. The Kaplan-Meier method was used to perform the survival analysis. Receiver operating characteristic (ROC) analysis was

Fig. 1 Representative case of relationship between MTV_{30%}, TLG_{30%} on ¹⁸F-FDG PET and recurrence. **a** A 53-year-old female was diagnosed with lung adenocarcinoma in right lower lung (T2a, stage IB). Lung lesion showed mild FDG uptake with SUVmax 2.3, MTV_{30%} 15.3, TLG_{30%} 17.9. Patient was followed up for 33.9 months without recurrence. **b** A 72-year-old female was diagnosed with lung

adenocarcinoma in right upper lung (T2a, stage IIB). Lung lesion showed mild FDG uptake with SUVmax 2.6, MTV_{30%} 29.5, TLG_{30%} 37.0. Patient experienced the recurrence 15.3 months after lobectomy. The SUV values ranged from 0.00 to 5.00 and CT Hounsfield unit (HU) values ranged from −1400 to 200

performed to calculate the area under the ROC curve (AUC) for each PET parameters. The log-rank test and Cox regression analysis were performed to evaluate the relationships between the categorical variables and RFS. Hazard ratios (HR) with 95% confidence intervals (CI) were determined in the multivariate Cox regression analysis.

Results

Patients Characteristics

Clinicopathologic characteristics of 149 patients are listed in Table 1. Of the 149 patients who were evaluated retrospectively, 70 (49%) were male and 79 (53%) were female with a mean age of 65.81 ± 8.44 years. The median follow-up time was 45.4 months (range 3.0–99.6 months). One hundred forty-two (95.3%) patients underwent lobectomy and 7 patients (4.7%) underwent wedge resection. Forty-nine patients

(32.9%) had a smoking history (ex- and current smoking). The mean number of dissected lymph nodes was 14.36 ± 7.61 . The mean of whole tumor size was 2.93 ± 1.52 cm. Thirty-eight patients (25.5%) had lymph node metastasis; 17 (11.4%) were N1 and 21 (14.1%) were N2.

Preoperative PET Parameter Analysis

Among the 149 patients of the entire cohort, the mean SUVmax of primary tumor was 4.79 ± 2.94 (mean $\pm$ standard deviation). We performed a comparison analysis for the PET parameters between the non-recurrence group and the recurrence group (Table 2). SUVmax (4.39 ± 2.85 vs. 5.47 ± 3.01 , $p = 0.034$) and MTV_{30%} (16.22 ± 24.97 vs. 25.30 ± 23.75 , $p = 0.030$) of the recurrence group were statistically significantly higher than those of the non-recurrence group. MTV_{30%} and TLG_{30%} showed a strongly positive correlation, with Pearson correlation coefficient of 0.771 ($p < 0.001$). The mean TLG_{30%} of the recurrence group was higher than that of the non-recurrence group (46.09 ± 101.30 vs. 75.15 ± 101.02 , $p = 0.096$).

ROC curve analysis was performed to define the optimal cut-off value of PET parameters for predicting recurrence (Table 3). In the ROC curve analysis, the AUC of TLG_{30%} for the recurrence was the highest compared with the AUCs of SUVmax, MTVs, and TLGs. MTVs and TLGs with a threshold value of 30% of SUVmax showed larger AUCs than those of MTVs and TLGs with a threshold value of 40%, and 50% of SUVmax. Therefore, we chose the MTV_{30%} and TLG_{30%} models to compare the prognostic value for predicting recurrence between MTV and TLG. The optimal cut-off value was 4.22 (sensitivity 60.4%, specificity 57.3%), 11.07 (sensitivity 62.3%, specificity 57.3%), and 30.56 (sensitivity 60.4%, specificity 57.3%) for SUVmax, MTV_{30%}, and TLG_{30%}, respectively; 74 patients (49.7%) showed SUVmax above 4.22, 73 patients (49.0%) showed MTV_{30%} above 11.07, and 60 patients (40.3%) showed TLG_{30%} above 30.56 (Table 3). According to the cut-off values of MTV_{30%} and TLG_{30%}, we divided the entire patient cohort into two groups and performed the comparison analysis between the two groups (Table 4). There was a significant difference in stage between high-MTV_{30%} and low-MTV_{30%} groups ($p < 0.001$) and between the high-TLG_{30%} and low-TLG_{30%} groups ($p = 0.020$).

Recurrence-Free Survival Analysis

Recurrence was observed in 53 patients (35.6%) as follows: 20 cases of loco-regional recurrence (1 resection margin or bronchus, 5 pleura, 5 mediastinum, and 14 ipsilateral lung, with 6 cases involving two sites), and 33 case of distant metastasis (18 lung, 6 bone, 4 brain, 3 extrathoracic lymph nodes, 2 liver, 1 adrenal gland, and 1 spinal cord, with 16 cases of multiple metastases). The median RFS time was 35.4 months;

Table 1 Characteristics of patients

Variables	All patients ($n = 149$)	%
Age at operation (years)	65.81 ± 8.44	
Sex		
Male	70	47.0%
Female	79	53.0%
Tumor size (cm)	2.93 ± 1.52	
No. of dissected lymph nodes	14.36 ± 7.61	
Smoking history		
Non-smoking	100	67.1%
Smoking	49	32.9%
Resection		
Wedge resection	7	4.7%
Lobectomy	142	95.3%
pT stage		
T1a/T1b	32/57	21.5%/38.3%
T2a/T2b	33/9	22.1%/6.0%
T3	18	12.1%
pN stage		
N0/N1	111/17	74.5%/11.4%
N2	21	14.1%
Visceral pleura invasion		
Absent	43	28.9%
Present	106	71.1%
Lymphovascular invasion		
Absent	134	89.9%
Present	15	10.1%
Adjuvant treatment		
None	83	55.7%
Chemo or radiotherapy	66	44.3%

Table 2 PET parameters of 149 patients

Variables	All patients (<i>n</i> = 149)	Non-recurrence (<i>n</i> = 96)	Recurrence (<i>n</i> = 53)	<i>P</i> value
SUVmax	4.79 ± 2.94	4.39 ± 2.85	5.47 ± 3.01	0.034
MTV _{30%}	19.45 ± 24.85	16.22 ± 24.97	25.30 ± 23.75	0.030
MTV _{40%}	14.05 ± 18.06	11.92 ± 17.83	17.90 ± 17.98	0.053
MTV _{50%}	9.70 ± 12.42	8.44 ± 12.22	11.98 ± 12.56	0.096
MTV _{2.0}	13.85 ± 27.46	10.36 ± 24.46	20.17 ± 31.47	0.036
TLG _{30%}	56.43 ± 101.88	46.09 ± 101.30	75.15 ± 101.20	0.096
TLG _{40%}	45.60 ± 85.21	38.43 ± 86.11	58.60 ± 82.77	0.167
TLG _{50%}	41.76 ± 100.20	39.46 ± 115.33	45.92 ± 65.16	0.707
TLG _{2.0}	53.56 ± 127.47	41.32 ± 122.28	75.73 ± 134.73	0.115

All data represent means ± standard deviation

Kaplan-Meier survival analysis showed that the 1-year, 2-year, and 5-year RFS rates were 92.4, 79.9, and 56.9%, respectively (Fig. 1a). The 1-year RFS rate was 96.6% in low-MTV_{30%} patients compared with 86.2% in high-MTV_{30%} patients ($p = 0.018$, Fig. 1b) and 96.0% in low-TLG_{30%} patients compared with 88.5% in high-TLG_{30%} patients ($p < 0.001$, Fig. 1c).

Risk Factors for Recurrence-Free Survival

In univariate analysis, high LNR, high MTV_{30%}, high TLG_{30%}, advanced stage, and lymphovascular invasion were risk factors for RFS (Table 5). On analysis using the TLG_{30%} model, which included TLG_{30%}, LNR, stage, and lymphovascular invasion, TLG_{30%} (HR 2.783; $p < 0.001$) and lymphovascular invasion (HR 10.006; $p = 0.001$) were the independent risk factors for RFS. On analysis of the MTV_{30%} model, which included MTV_{30%}, LNR, stage, and lymphovascular invasion, lymphovascular invasion (HR 8.865, $p = 0.002$) was observed to be the only independent risk factor for RFS, and MTV_{30%} showed marginal significance (HR 2.071; $p = 0.059$) (Fig. 2).

Discussion

In this study, we found that TLG_{30%} value was an independent prognostic factor for RFS in patients with stage I–IIIA lung adenocarcinoma treated by surgical resection. Recurrence is one of most common causes of treatment failure in patients after surgery for NSCLC. Despite the early stage of NSCLC, up to 30% of NSCLC patients experience recurrence during follow-up, and this recurrence is strongly related to poor OS [3, 4]. It has been reported that several clinicopathologic prognostic factors such as sex (male), old age, high lymph node stage, lymphovascular invasion, and histologic grade were strongly correlated with poor RFS and OS [3, 6, 18, 19]. As reported in the literature, adenocarcinoma is the predominant

histologic type in NSCLC [20]. There is a need for additional prognostic markers to identify patients who require adjuvant therapy for early-stage NSCLC after curative treatment. The latest National Comprehensive Cancer Network guidelines define that patients for high risk for poorly differentiated cancer, visceral pleural involvement, vascular invasion, tumor size > 4 cm, wedge resection, and unknown lymph node status [21]. These patients may be potential candidates for postoperative adjuvant chemotherapy.

The prognostic value of volume-base PET parameters, which is independent of the TNM stage, has been widely studied in NSCLC [9–13, 22–25]. MTV defines the volume of a metabolically active tumor, and TLG is measured by multiplying the MTV with the mean SUV; thus, an approach involving the use of MTV and TLG combines the volumetric and metabolic information of primary tumor lesion from ¹⁸F-FDG PET. SUVmax may be a surrogate marker for tumor aggressiveness [26, 27]; however, it could be affected by the biologic (serum glucose level, body weight, fasting time) and technologic factors (image acquisition time, reconstruction method). Tumor volume may be important not only in advanced-stage but also in early-stage NSCLC. Regarding the clinical significance of MTV and TLG in stage I lung adenocarcinoma, two recent studies have been reported. Wang et al. [13] reported that among SUVmax, SUVmean, SUVpeak, MTV, and TLG, only MTV was an independent prognostic factor for progression; this study analyzed stage I NSCLC in 127 patients and applied the 2 PET delineation methods according to different pulmonary nodule types. The methods used for solid lesions was adaptive target volume delineation using adaptive iterative algorithm; the method used for non-solid and part-solid lesions was adaptive thresholding at 40% SUVmax, which adapts the threshold value inside the selected VOI relative to the mean background SUV.

Park et al. [12] evaluated preoperative SUVmax and TLG in 248 patients with stage IA NSCLC that was treated by surgical resection; in multivariate analysis for OS using the

Table 3 Area under the curve of MTV and TLG measured by fixed threshold value of various SUVmax %

Variable	Area under the curve	Cut-off value	Sensitivity (%)	Specificity (%)
SUVmax	0.616 (0.522~0.710)	4.22	60.4	57.3
MTV _{30%}	0.634 (0.538~0.730)	11.07	62.3	57.3
MTV _{40%}	0.605 (0.505~0.705)	7.37	60.4	53.1
MTV _{50%}	0.594 (0.496~0.691)	4.96	58.5	52.1
MTV _{2.0}	0.655 (0.563~0.747)	5.64	60.4	59.4
TLG _{30%}	0.683 (0.592~0.773)	30.56	60.4	57.3
TLG _{40%}	0.667 (0.576~0.758)	16.06	67.9	53.1
TLG _{50%}	0.659 (0.567~0.750)	15.27	64.2	64.6
TLG _{2.0}	0.659 (0.566~0.751)	15.65	60.4	62.5

SUVmax model and TLG model, the concordance index of the TLG model was slightly higher than that of the SUVmax model. They used the threshold value of SUV2.5 and analyzed only stage IA patients; thus, the small size of stage IA NSCLC lesions may have influenced the MTV by partial-volume effects. Even though these two studies analyzed stage I lung adenocarcinoma, the clinical implication of volume-based PET parameters was controversial. In addition, a fixed threshold value of SUV2.5 or 50% of SUVmax of the primary tumor were mainly used as the threshold intensity values [12, 28, 29], and 40% of threshold values showed the best performance for defining the tumor volume [30]. We also analyzed

the predictive value of recurrence with MTV_{2.0} and TLG_{2.0} values. MTV_{2.0} (10.36 ± 24.46 vs. 20.17 ± 31.47 , $p = 0.036$) of the recurrence group were statistically significantly higher than those of the non-recurrence group. In univariate analysis, high MTV_{2.0} and high TLG_{2.0} were risk factors for RFS (supplement 1). In multivariate analysis, TLG_{2.0} (HR, 7.325; $p = 0.004$) was the independent risk factors for RFS. However, in 43 patients (28.9%) of our cohort, MTV_{2.0} values were measured to be less than 1 cm³. SUV2.0 as threshold value to calculate the MTV and TLG showed relatively high cut-off value in our study. Lung adenocarcinoma showed a significantly lower value of SUVmax, MTV, and TLG than those of

Table 4 Patients characteristics with MTV_{30%} and TLG_{30%} value

	MTV _{30%} > 11.07	MTV _{30%} ≤ 11.07	P value	TLG _{30%} > 30.56	TLG _{30%} ≤ 30.56	P value
Age			0.190			0.318
> 65	43 (28.9%)	36 (24.2%)		35 (23.5%)	44 (29.5%)	
≤ 65	30 (20.1%)	40 (26.8%)		25 (16.8%)	45 (30.2%)	
Smoking			0.863			0.374
Non-smoker	50 (33.6%)	51 (34.2%)		38 (25.5%)	63 (42.3%)	
Ex- or current smoker	23 (15.4%)	25 (16.8%)		22 (14.8%)	26 (17.4%)	
Tumor site			0.870			0.406
Right	40 (26.9%)	43 (28.9%)		36 (24.2%)	47 (31.5%)	
Left	33 (22.1%)	33 (22.1%)		24 (16.1%)	42 (28.2%)	
LNR			0.467			0.317
> 0.15	11 (7.4%)	8 (5.4%)		10 (6.7%)	9 (6.0%)	
≤ 0.15	62 (41.6%)	68 (45.6%)		50 (33.6%)	80 (53.7%)	
Stage			< 0.001			0.020
I	8 (5.4%)	85 (57.0%)		30 (20.1%)	63 (42.3%)	
II	10 (6.7%)	18 (12.1%)		17 (11.4%)	11 (7.4%)	
III	9 (6.0%)	19 (12.8%)		13 (8.7%)	15 (10.1%)	
Visceral pleural invasion			0.284			0.270
Absent	18 (12.1%)	25 (16.8%)		14 (9.4%)	29 (19.5%)	
Present	55 (36.9%)	51 (34.2%)		46 (30.9%)	60 (40.2%)	
Lymphovascular invasion			0.179			0.592
Absent	63 (42.3%)	71 (47.6%)		53 (35.5%)	81 (54.4%)	
Present	5 (3.4%)	10 (6.7%)		7 (4.7%)	8 (5.4%)	

Table 5 Univariate and multivariate analysis for predicting the recurrence

Univariate analysis			Multivariate analysis		
Variable	OR (95% CI)	<i>p</i>	MTV _{30%}		TLG _{30%}
			OR (95% CI)	<i>p</i>	<i>p</i>
Age (> 65 vs. ≤ 65)	0.879 (0.449–1.720)	0.706			
Sex (male vs. female)	0.884 (0.516–1.515)	0.884			
Smoking history (none vs. ex- or current)	1.363 (0.769–2.417)	0.289			
LNR (> 0.15 vs. ≤ 0.15)	3.941 (2.071–7.498)	< 0.001	2.480 (0.660–9.314)	0.179	1.980 (0.513–7.639)
SUVmax (> 4.22 vs. ≤ 4.22)	1.826 (0.927–3.597)	0.082			
MTV _{30%} (> 11.07 vs. ≤ 11.07)	1.931 (1.110–3.360)	0.020	2.071 (0.973–6.007)	0.059	
TLG _{30%} (> 30.56 vs. ≤ 30.56)	2.828 (1.627–4.915)	< 0.001			2.783 (1.567–4.785)
Stage (≥ III vs. I, II)	2.746 (1.533–4.919)	0.001	2.001 (0.667–6.007)	0.216	2.561 (0.831–7.910)
Visceral pleura invasion (absent vs. present)	1.096 (0.610–1.972)	0.759			
Lymphovascular invasion (absent vs. present)	3.514 (1.841–6.710)	< 0.001	8.865 (2.210–35.561)	0.002	10.006 (2.415–41.448)
Adjuvant treatment (none vs. chemo- or radiotherapy)	1.454 (0.845–2.504)	0.177			

squamous cell carcinoma [14, 15]; we further analyzed the prognostic value of MTVs and TLGs using the lower threshold value of 30% of SUVmax of the primary tumor.

Lung adenocarcinoma consists of various histologic subtypes. The predominant histologic subtypes of adenocarcinoma are acinar, lepidic, papillary, micropapillary, solid, and mucinous type. A recent study reported the differences in GLUT1 expression and the prognostic potential of FDG-PET according to the histologic subtypes of NSCLC. The micropapillary and solid histologic subtypes of lung adenocarcinoma were associated with GLUT1 expression, and high MTV and TLG values were associated with the solid histology. However, the majority of subtypes of adenocarcinoma in our study were acinar (57.5%). These histologic subtypes showed a relatively lower GLUT1 expression and ¹⁸F-FDG uptake. In addition, micropapillary (5.7%) and solid (11.4%)

histology constituted a lower proportion of entire cohort, respectively. This may be attributed to the effect of the lower value of MTVs and TLGs of the primary tumor in our entire cohort.

In a previous study, Kim et al. [11] reported that MTV was a better predictor for RFS and OS compared with TLG in NSCLC stage I to IIIA treated by surgical resection. There were no significant differences among the MTVs calculated by various threshold values of SUV (2.5, 3.0, 3.5, and 4.0). We expected that MTV using the lowest threshold value of 30% SUVmax would be an independent prognostic factor for the RFS in lung adenocarcinoma patients. In our study, TLG_{30%} showed the largest AUC among the AUCs of SUVmax, MTVs, and TLGs. In the MTV_{30%} model, MTV_{30%} showed marginal significance (*p* = 0.059). TLG_{30%} was an independent predictor for RFS; it showed a larger

Fig. 2 Recurrence-free survival rate **a** in entire study population and recurrence-free survival rate base on **b** MTV_{30%} > 11.07 and MTV_{30%} ≤ 11.07 and **c** TLG_{30%} > 30.56 and TLG_{30%} ≤ 30.56

AUC compared with $MTV_{30\%}$. This result was consistent with the findings of a previous study [12]. Our data demonstrated that TLG was a significant prognostic factor not only for stage IA lung adenocarcinoma but also for up to stage IIIA patients treated by surgical resection. Although TLG was an independent prognostic factor for RFS in lung adenocarcinoma stage I to IIIA treated by surgical resection, SUVmax and MTV remain useful parameters for prediction recurrence, and this was demonstrated in previous studies involving a large number of lung adenocarcinoma patients treated by surgical resection.

This study has limitations. First, it was a retrospective, single-center study with a relatively small population by single PET/CT equipment. Further study of a larger number of patients and comparison study with other PET/CT equipment are needed to confirm whether TLG is a better predictive factor. Also, in this study, the overall survival observation period was not long enough. Therefore, a relatively long follow-up observation period should be considered for long-term survival analysis. Despite these limitations, this present study provides meaningful results by analyzing volume-based parameters using a threshold value of 30% of SUVmax for predicting RFS in stage I to IIIA lung adenocarcinoma treated by surgical resection.

Conclusion

High $TLG_{30\%}$ was observed to be a significant risk factor for low RFS in patients treated using surgical resection for stage I to IIIA lung adenocarcinoma. Patients with high $TLG_{30\%}$ at the preoperative PET study should be closely observed for recurrence.

Compliance with Ethical Standards

Conflict of Interest Sunju Choi, Hye Ryeong Kwon, Hee Young Cho, Kisoo Pahk, Sung-Ho Lee, Jae-Ho Chung, Hyun Woo Kwon, and Sungeun Kim declare that they have no conflict of interest.

Ethical Statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Informed Consent The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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