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Evaluation of maximum standardized uptake value at fluorine-18 fluorodeoxyglucose positron emission tomography as a complementary T factor in the eighth edition of lung cancer stage classification

Hyungjin Kim[a,b], Jin Mo Goo[a,b,c], Jin Chul Paeng[d], Young Tae Kim[c,e], Chang Min Park[a,b,c,*]

[a] Department of Radiology, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
[b] Institute of Radiation Medicine, Seoul National University Medical Research Center, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
[c] Cancer Research Institute, Seoul National University, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
[d] Department of Nuclear Medicine, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea
[e] Department of Thoracic and Cardiovascular Surgery, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea

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ABSTRACT

Objectives: This retrospective cohort study aimed to analyze the prognostic effect of maximum standardized uptake value (SUVmax) as a complementary T factor in addition to the clinical T category of the eighth-edition staging system for the prediction of disease-free survival (DFS) in patients with resected lung adenocarcinomas.
Materials and methods: A total of 572 patients (male:female = 235:337; median age, 64 years) with clinical stage I (T1-T2aN0M0) adenocarcinomas underwent preoperative fluorine-18 fluorodeoxyglucose positron emission tomography and subsequent lobectomy between 2009 and 2015. The prognostic values of SUVmax and $_{PET}$T category [categorized SUVmax; $_{PET}$T1 (SUVmax ≤2), $_{PET}$T2 (2 < SUVmax ≤7), and $_{PET}$T3 (SUVmax > 7)] in conjunction with the clinical T category were analyzed using a multivariable Cox regression and a likelihood-ratio test, respectively. The clinical T category was then upstaged or downstaged ($cT_{Modified}$) based on $_{PET}$T. This new categorization system was evaluated using a Cox regression and then compared with the clinical T category.
Results: Multivariable-adjusted Cox regression revealed that SUVmax and $_{PET}$T were independent and significant predictors with the current clinical T category for DFS. Regarding SUVmax, the adjusted hazard ratio (HR) was 1.048 (95% CI: 1.009, 1.089; P = 0.017). Regarding $_{PET}$T, the adjusted HRs were 2.365 (95% CI: 1.034, 5.406; P = 0.041) in $_{PET}$T2 and 3.005 (95% CI: 1.258, 7.179; P = 0.013) in $_{PET}$T3. The inclusion of the PET-derived factors substantially improved the model fit (P < 0.05). $cT_{Modified}$ was a significant predictor of DFS, which improved the prognostic discrimination of lung adenocarcinomas.
Conclusion: SUVmax and $_{PET}$T are independent prognostic factors after adjustment for the clinical T category. The $_{PET}$T category could be used to adjust the clinical T category preoperatively.

1. Introduction

Stage classification is an essential element in cancer diagnosis, therapeutic decision-making, and prognostication. The Tumor-Node-Metastasis (TNM) staging model has been the universal modality used to describe the extent of the disease and to categorize tumor [1]. The eighth edition of the American Joint Committee on Cancer (AJCC) staging system for lung cancer was introduced in 2017. A distinguishing feature of this revised staging system is that the clinical T categorization is based on the tumor size determined by the largest dimension of the solid portion in computed tomography (CT) and the pathologic T categorization is based on the invasive component in microscopy [2].

Standardized uptake value (SUV), which is measured at fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET)/CT, is a well-known prognostic factor in patients with lung cancers [3]. Several previous studies analyzed the prognostic power of SUV for predicting

Abbreviations: AIC, Akaike's information criterion; AJCC, American Joint Committee on Cancer; $cT_{Modified}$, modified clinical T categorization using the $_{PET}$T category; FDG-PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; HR, hazard ratio; IQR, interquartile range; $_{PET}$T, T categorization using the maximum standardized uptake value obtained from fluorine-18 fluorodeoxyglucose positron emission tomography; SUVmax, maximum standardized uptake value; TNM, Tumor-Node-Metastasis

* Corresponding author at: Department of Radiology, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, 03080, Republic of Korea.
E-mail address: cmpark.morphius@gmail.com (C.M. Park).

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survival in lung cancer patients at various stages and histologies and in those treated using different modalities [4–11]. Indeed, maximum SUV (SUVmax) was included in the International Association for the Study of Lung Cancer (IASLC) database as a nonanatomical element to prepare for the development of a prognostic index that integrates both anatomical and nonanatomical elements [12].

Nevertheless, the role of SUVmax in clinical staging as a potential nonanatomical T factor in the eighth-edition staging system has not yet been demonstrated. The analysis of SUVmax with the clinical T category of the eighth edition as a covariate is particularly important because SUVmax has been shown to be significantly correlated with the invasive component of lung adenocarcinomas [13–15]. Considering that the solid portion size on CT scans, the current T factor, is a surrogate for the pathologic invasive component [2], it remains unclear whether SUVmax can still be used as an independent prognostic factor in the era of the eighth-edition T coding system. If SUVmax has retained its independent prognostic value, it could be used as a complementary T factor to increase the accuracy of risk stratification and therapeutic planning (i.e., selection of candidates for sublobar resection).

Therefore, we aimed to analyze the prognostic value of SUVmax as a continuous or categorical variable in addition to the current clinical T category for the prediction of disease-free survival (DFS) in patients who had undergone complete surgical resection for stage I lung adenocarcinomas.

2. Materials and methods

This retrospective analysis was approved by the Institutional Review Board of Seoul National University Hospital, and the requirement of written informed consent was waived. Our study population (572/572) was reported previously [16]. In the prior study, we compared the prognostic performances of clinical T categorization between the longest and average diameter measurements on CT scans. The current study analyzed the prognostic implication of SUVmax as a complementary T factor for clinical staging.

2.1. Study population

A total of 2360 consecutive patients underwent curative surgical resection for lung cancer without preoperative chemotherapy and/or radiotherapy between January 2009 and December 2015 at our hospital, which is a tertiary referral center. Of these patients, 745 patients with clinical stage I (T1-T2aN0M0) lung adenocarcinomas, who had undergone complete resection by lobectomy and had no synchronous or metachronous lung cancers, were identified by searching the electronic medical records (EMR). Our study population was determined based on the following exclusion criteria: 1) patients without preoperative FDG-PET/CT (n = 40); 2) patients with FDG-PET/CT taken more than 90 days before surgery (n = 8); and 3) SUVmax not recorded in the nuclear medicine report (n = 125). Consequently, 572 patients were included in this study (Fig. 1).

2.2. Data collection

Data were collected from the EMRs regarding patient characteristics (age and sex), smoking status (never smoker or ex-/current smoker), history of malignancy prior to lung surgery (presence or absence), family history of lung cancer (presence or absence), date of surgery, date of preoperative chest CT scan, date of preoperative FDG-PET/CT, nodule location (upper lobe or other lobes) and pathological diagnosis. The nodule type (part-solid or solid) was obtained from the radiology report in the picture archiving and communication system (PACS; INFINITT PACS, INFINITT Healthcare, Seoul, Korea).

The sizes of the nodules (i.e., the solid portion) was measured after review of all CT images by one of two trained radiology technicians (either M.L. with 7 years of research experience in chest CT or J.Y.J. with one year of research experience in chest CT) under the supervision of a board-certified thoracic radiologist (H.K. with 8 years of CT experience). Thus, all nodules were measured once. The longest diameter was measured at the axial plane using the lung window setting [window width, 1500 Hounsfield units (HU); level, -700 HU] with the electronic calipers in PACS according to the staging system [2]. All image reviewers were blinded to the pathologic diagnosis and patient outcome. The solid portion size was recorded in centimeters, including millimeter increments. The clinical T category (from cT1a to cT2a) was then determined using the solid portion size according to the eighth edition of the AJCC staging system for lung cancer [1,2].

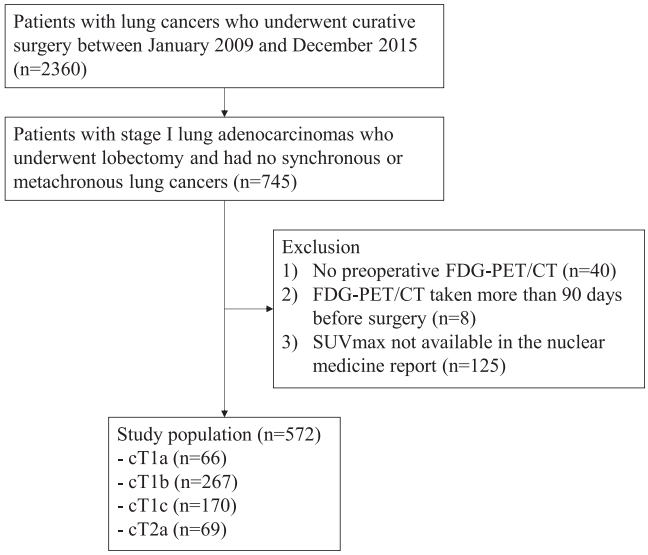

Fig. 1. Flow diagram of patient inclusion and exclusion.
FDG-PET/CT = fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; SUVmax = maximum standardized uptake value.

The SUVmax of lung cancer was acquired from the nuclear medicine report in PACS. It was automatically calculated from the spherical volume of interest drawn over the lesions using the dedicated software packages provided by the vendors. The SUVmax was trichotomized using quartiles (the 25th and 75th percentiles; 2 and 7) to convert SUVmax into a categorical variable as a complementary T factor [hereafter, $_{PET}$T category; $_{PET}$T1 (SUVmax $\leq$2), $_{PET}$T2 (2 < SUVmax $\leq$7), and $_{PET}$T3 (SUVmax > 7)] for the clinical staging [12,17].

In this study, the modified clinical T category ($cT_{Modified}$) was devised to utilize the $_{PET}$T category as a stage-shifting parameter. Specifically, after confirming that the clinical T and $_{PET}$T categories were significant and independent prognostic factors (see Results), the $_{PET}$T category was used to upshift (for $_{PET}$T3) or downshift (for $_{PET}$T1) the clinical T categories (Supplementary Fig. 1). For example, cT1b with $_{PET}$T1 (SUVmax $\leq$2) was downshifted (one subcategory down) to $cT_{Modified}$1a, and cT1b with $_{PET}$T3 (SUVmax > 7) was upshifted (one subcategory up) to $cT_{Modified}$1c. The clinical T categories of lung cancers with $_{PET}$T2 were unchanged.

The primary end point used in this study was DFS, which was measured from the date of surgery to the date of the first recorded evidence of clinical (local or regional) recurrence and/or distant metastasis as confirmed by imaging, histologic evidence, or death by any cause [18]. The time of censoring was determined as the date of the last chest CT scan.

2.3. CT image acquisition

CT scans were performed using nine different scanners produced by four manufacturers [Brilliance 64, Ingenuity, and iQon, Philips Healthcare, Best, Netherlands; LightSpeed Ultra and Discovery

CT750HD, GE Healthcare, Waukesha, WI, USA; Somatom Sensation 16, Definition, and Force, Siemens Healthcare, Forchheim, Germany; Aquilion One, Toshiba Medical Systems (now Canon Medical Systems), Otawara, Japan]. Our hospital is a tertiary medical center, and it operates multiple CT scanners that are purchased from various vendors. Thus, heterogeneity in imaging acquisition was inevitable during the retrospective data collection. All the patients underwent CT scans from the lung apex to base at suspended maximum inspiration. The scans were performed at 120 kVp and at mAs values ranging from approximately 20 to 200 mAs with or without the automatic exposure control of each vendor. The CT scans were reconstructed with a slice thickness ≤5 mm. For patients with part-solid nodules, the slice thickness was less than or equal to 1.5 mm.

2.4. FDG-PET/CT acquisition

Whole-body ^{18} F-FDG-PET/CT scans were obtained using three scanners (TruePoint 40, mCT 40, and mCT 64, Siemens Healthcare, Erlangen, Germany) from a single vendor. The patients fasted for at least 6–8 h before FDG was injected intravenously. The patients were administered FDG (5.18 MBq/kg), and the images were acquired 60 min after administration. The CT images were obtained from the skull base to the proximal thigh and emission scans followed over the same body region for 1–2 min per bed position. Attenuation-corrected PET images were reconstructed using iterative reconstruction algorithms.

2.5. Pathologic diagnosis

Pathological diagnoses in 71.2% (407/572) of the study population were established by the attending pathologists at our hospital according to the 2011 lung adenocarcinoma classification described by the IASLC/American Thoracic Society/European Respiratory Society [19]. Because the pathological diagnoses were determined as a part of routine clinical practice, and the specimens were not reviewed specifically for this study, 28.8% (165/691) of the patients were diagnosed before the implementation of the 2011 adenocarcinoma classification.

2.6. Statistical analysis

A Cox regression analysis was performed to validate the prognostic performance of SUVmax in conjunction with the current clinical T category based on the solid portion size. Univariable analyses of the prognostic factors were followed by multivariable analyses using input variables with P-values less than 0.10 in the univariable analyses. Backward stepwise elimination was used as the model selection procedure based on Akaike's information criterion (AIC) [20,21]. In this study, three multivariable Cox models were constructed: 1) without PET-derived factors (model 1); 2) with SUVmax (a continuous variable; model 2); 3) with $_{PET}$T category (model 3). This approach was adopted to identify the significance of the hazard ratios (HR) of the clinical T category with and without the PET-derived factors and to compare the goodness-of-fit of the three models. The model fit was compared using the likelihood-ratio test. AIC was also used to compare the model fit; a lower AIC represented a better fit [22].

The number of patients in each conventional cT and $cT_{Modified}$ category was calculated and then compared using the McNemar–Bowker test. A Cox regression analysis was then performed with $cT_{Modified}$ to demonstrate the significance of this categorization system. AIC and Harrell's concordance index were calculated and compared between cT and $cT_{Modified}$.

All the statistical analyses were performed using the SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) and R software, version 3.5.1 (http://www.R-project.org; package: smooth HR, survival, and survminer). A P-value < 0.05 was considered to indicate statistical significance. Data imputation was not performed for the missing values.

Table 1
Patient and Nodule Characteristics.

Variable		No. of Patients (n = 572)
Age (years)[a]		64 (56, 70)
Sex	Male	235 (41.1)
	Female	337 (58.9)
Past history of malignancy other than lung cancer[b]	Yes	91 (15.9)
	No	454 (79.4)
Family history of lung cancer[c]	Yes	32 (5.6)
	No	526 (92.0)
Smoking history[d]	Never smoker	364 (63.6)
	Ex- or current smoker	207 (36.2)
Nodule location	Upper lobes	312 (54.5)
	Other lobes	260 (45.5)
Nodule type	Part-solid	241 (42.1)
	Solid	331 (57.9)
Clinical T category[e]	cT1a	66 (11.5)
	cT1b	267 (46.7)
	cT1c	170 (29.7)
	cT2a	69 (12.1)
SUVmax[a]		4.0 (2.2, 7.2)
Pathology	Adenocarcinoma in situ	5 (0.9)
	Minimally invasive adenocarcinoma	8 (1.4)
	Invasive adenocarcinoma	559 (97.7)
Cancer recurrence or deaths		101 (17.7)
Disease-free survival (days)[a]		1132 (737, 1784)
CT-to-surgery interval (days)[a]		15 (3, 24)
FDG-PET/CT-to-surgery interval (days)[a]		14 (8, 23)

Note.– Unless otherwise specified, numbers in parentheses are percentages. FDG-PET/CT = fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; SUVmax = maximum standardized uptake value; TNM = Tumor-Node- Metastasis.

[a] Data are median with interquartile range in parentheses.

[b] Data were not available in 27 patients (4.7%).

[c] Data were not available in 14 patients (2.4%).

[d] Data were not available in 1 patients (0.2%).

[e] Clinical T categorization based on the eighth-edition TNM classification for lung cancer.

3. Results

Our study population included 235 males [median age, 66 years; interquartile range (IQR): 58, 71 years] and 337 females (median age, 63 years; IQR: 55, 70 years; Mann-Whitney U test, P = 0.027). The median age of the entire study population was 64 years (IQR: 56, 70 years). The patient characteristics are described in Table 1.

Clinical T categories were cT1 in 66 (11.5%) patients, cT1b in 267 (46.7%) patients, cT1c in 170 (29.7%) patients, and cT2a in 69 (12.1%) patients. $_{PET}$T1 (SUVmax ≤2) were observed in 124 (21.7%) patients, $_{PET}$T2 (2 < SUVmax ≤7) in 301 (52.6%) patients, and $_{PET}$T3 (SUVmax > 7) in 147 (25.7%) patients. Integration of the $_{PET}$T into the clinical T category ($cT_{Modified}$) resulted in category shifts in 189 patients (33%). Importantly, 70 patients (12.2%) were upstaged to stage IB from stage IA, while 4 patients (0.7%) were downstaged to stage IA from stage IB. The median SUVmax was 1.6 (IQR: 1.3, 2.2) in cT1a, 3.2 (IQR: 2.1, 5.4) in cT1b, 5.8 (3.6, 9.1) in cT1c, and 7.3 (IQR: 4.4, 11.9) in cT2a. The percentages of recurrences according to the clinical T and $_{PET}$T categories are described in Supplementary Table 1.

3.1. Univariable and multivariable Cox regression analysis

Table 2 shows the results of the univariable Cox regression analysis. The variables that showed P-values less than 0.10 were age, sex, smoking status, nodule type, clinical T category, SUVmax, and $_{PET}$T category. These variables were then used as candidates for the subsequent multivariable analyses. SUVmax was in a linear relationship to

Table 2
Univariable Cox Regression Analysis for Disease-Free Survival in Lung Adenocarcinomas.

Variable	Subcategory	HR	95% CI of HR	P-value
Age (year)		1.024	1.002, 1.047	0.030
Male sex		1.546	1.046, 2.285	0.029
Past history of cancer		1.381	0.840, 2.269	0.203
Family history of lung cancer		1.763	0.854, 3.639	0.125
Ex- or current smoker (reference: never smoker)		1.558	1.052, 2.308	0.027
Location at upper lobes (reference: other lung lobes)		0.795	0.538, 1.174	0.248
Solid nodule (reference: part-solid nodule)		1.922	1.249, 2.958	0.003
cT (reference: cT1a)	cT1b	2.523	0.771, 8.254	0.126
	cT1c	6.121	1.897, 19.757	0.002
	cT2a	10.305	3.109, 34.150	< 0.001
SUVmax		1.089	1.055, 1.123	< 0.001
$_{PET}$T (reference: $_{PET}$T1)	$_{PET}$T2	3.362	1.527, 7.403	0.003
	$_{PET}$T3	6.204	2.782, 13.835	< 0.001
$cT_{Modified}$ (reference: $cT_{Modified}$1a)	$cT_{Modified}$1b	3.378	1.284, 8.887	0.014
	$cT_{Modified}$1c	6.642	2.582, 17.090	< 0.001
	$cT_{Modified}$2a	10.058	3.966, 25.506	< 0.001

CI = confidence interval; cT = clinical T categorization; $cT_{Modified}$ = modified clinical T categorization using the $_{PET}$T category; HR = hazard ratio; $_{PET}$T = T categorization using the maximum standardized uptake value obtained from fluorine-18 fluorodeoxyglucose positron emission tomography; SUVmax = maximum standardized uptake value.

the log-hazard (Supplementary Fig. 2).

The multivariable Cox model (model 1), which was constructed without SUVmax or a $_{PET}$T category, showed that the adjusted HRs were 2.370 [95% confidence interval (CI): 0.723, 7.765; P = 0.154] for cT1b, 5.784 (95% CI: 1.790, 18.692; P = 0.003) for cT1c, and 9.528 (95% CI: 2.864, 31.691; P < 0.001) for cT2a. The second multivariable model (model 2), which was built with SUVmax (continuous variable), revealed that both cT and $_{PET}$T factors were significant independent predictors of DFS. The adjusted HRs were 2.171 (95% CI: 0.661, 7.131; P = 0.201) for cT1b, 4.533 (95% CI: 1.373, 14.970; P = 0.013) for cT1c, and 7.380 (95% CI: 2.174, 25.058; P = 0.001) for cT2a. The adjusted HR of SUVmax was 1.048 (95% CI: 1.009, 1.089; P = 0.017). The third model, which included the $_{PET}$T category (model 3), demonstrated that the latter was an independent and significant prognostic factor in addition to the cT category. The adjusted HRs were 1.630 (95% CI: 0.479, 5.545; P = 0.434) for cT1b, 3.332 (95% CI: 0.970, 11.447; P = 0.056) for cT1c, 5.324 (95% CI: 1.500, 18.899; P = 0.010) for cT2a, 2.365 (95% CI: 1.034, 5.406; P = 0.041) for $_{PET}$T2, and 3.005 (95% CI: 1.258, 7.179; P = 0.013) for $_{PET}$T3. The inclusion of the PET-derived factors substantially improved the model fits in model 2 and model 3 (P = 0.024 and 0.025, respectively). AICs were 1166.3 for model 1, 1163.2 for model 2, and 1162.9 for model 3. These results are listed in Table 3. The Kaplan–Meier survival curves stratified by cT and $_{PET}$T categories are shown in Fig. 2.

3.2. Modified clinical T category using $_{PET}$T as a stage-shifting parameter

The number of patients in each $cT_{Modified}$ category was significantly different from that in each conventional cT category (P < 0.001; Supplementary Table 2). The results of the Cox regression analysis revealed that the stage-shifting of cT categories according to the $_{PET}$T factor was statistically significant. For $cT_{Modified}$ (Fig. 3), the HRs were 3.378 (95% CI: 1.284, 8.887; P = 0.014) for $cT_{Modified}$1b, 6.642 (95% CI: 2.582, 17.090; P < 0.001) for $cT_{Modified}$1c, and 10.058 (95% CI: 3.966, 25.506; P < 0.001) for $cT_{Modified}$2a. The prognostic discrimination of $cT_{Modified}$1a and $cT_{Modified}$1b became feasible, which was not possible with the conventional cT (Table 2). The AIC of $cT_{Modified}$ was 1161.7, which was lower than that of the conventional cT (1168.5). The concordance index of $cT_{Modified}$ (0.68; 95% CI: 0.62, 0.73) was higher than that of the conventional cT (0.66; 95% CI: 0.61, 0.72).

4. Discussion

Our results revealed that SUVmax was an independent predictor of DFS in patients with surgically treated stage I lung adenocarcinomas. SUVmax could be utilized as an independent and complementary T factor ($_{PET}$T category) in conjunction with the clinical T category of the eighth-edition staging system. The addition of a $_{PET}$T factor significantly improved the model's fit for survival prediction. In addition, we demonstrated that the $_{PET}$T category could be used to upshift or downshift the clinical T category, which led to the improved prognostic discrimination of lung adenocarcinomas.

A recent multivariable, pooled meta-analysis of individual data, which assessed 1563 patients in 11 studies, showed that the addition of SUV to a model built using conventional prognostic factors, including age, stage, tumor size, and surgical treatment, was statistically

Table 3
Multivariable Cox Regression Analysis for Disease-Free Survival in Lung Adenocarcinomas.

		Model 1 (without PET-derived factors)			Model 2 (with SUVmax)			Model 3 (with $_{PET}$T category)		
Variable	Subcategory	HR	95% CI of HR	P-value	HR	95% CI of HR	P-value	HR	95% CI of HR	P-value
Ex- or current smoker (reference: never smoker)		1.515	1.022, 2.245	0.039	1.436	0.966, 2.134	0.073	1.422	0.951, 2.127	0.086
cT (reference: cT1a)	cT1b	2.370	0.723, 7.765	0.154	2.171	0.661, 7.131	0.201	1.630	0.479, 5.545	0.434
	cT1c	5.784	1.790, 18.692	0.003	4.533	1.373, 14.970	0.013	3.332	0.970, 11.447	0.056
	cT2a	9.528	2.864, 31.691	< 0.001	7.380	2.174, 25.058	0.001	5.324	1.500, 18.899	0.010
SUVmax					1.048	1.009, 1.089	0.017			
$_{PET}$T (reference: $_{PET}$T1)	$_{PET}$T2							2.365	1.034, 5.406	0.041
	$_{PET}$T3							3.005	1.258, 7.179	0.013

CI = confidence interval; cT = clinical T categorization; PET = positron emission tomography; HR = hazard ratio; $_{PET}$T = T categorization using the maximum standardized uptake value obtained from fluorine-18 fluorodeoxyglucose positron emission tomography; SUVmax = maximum standardized uptake value.

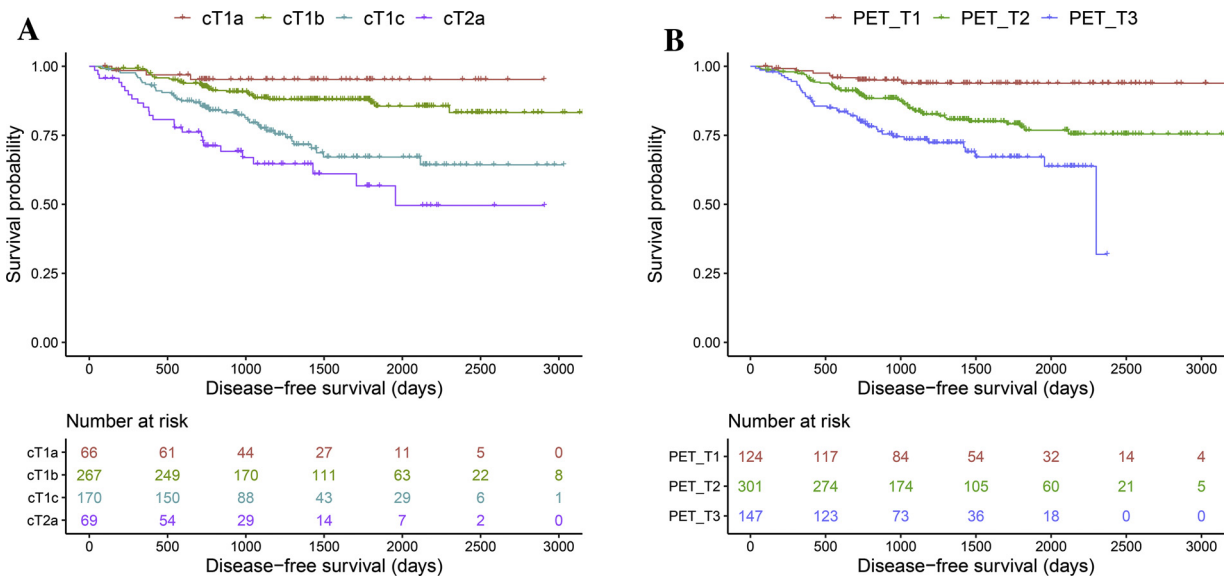

Fig. 2. Kaplan–Meier disease-free survival curves stratified by (A) the clinical T category according to the eighth-edition T coding system and (B) the proposed $_{PET}$T category.
$_{PET}$T = T categorization using the maximum standardized uptake value obtained from fluorine-18 fluorodeoxyglucose positron emission tomography.

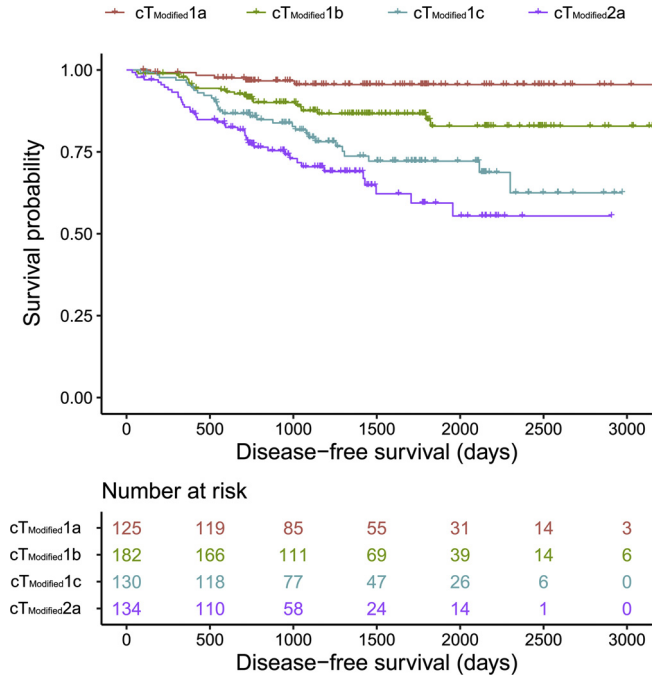

Fig. 3. Kaplan–Meier disease-free survival plot by the modified clinical T category, which utilized $_{PET}$T factor as a stage-adjusting parameter for stage I lung adenocarcinomas.
$_{PET}$T = T categorization using the maximum standardized uptake value obtained from fluorine-18 fluorodeoxyglucose positron emission tomography.

significant [3]. The adjusted HR of the dichotomous SUV category (high vs. low; median cutoff) was 1.58 (95% CI: 1.27, 1.96; P < 0.001) [3]. This meta-analysis, which included studies published in the early 2000s, was published before the implementation of the eighth-edition staging system, the T coding system of which is strikingly different from the previous editions. Furthermore, the usage of either the clinical or the pathological staging system is also unclear. Nevertheless, in this study, it was concluded that SUV was a potential independent prognostic marker in patients with stage I-III non-small cell lung cancers (NSCLCs). Several prior meta-analyses reached similar conclusions, suggesting the potential of SUV for the prognostication of NSCLCs [23–25].

In the seventh or earlier editions of the TNM staging system, the total tumor size was used, including ground-glass opacity, for determining the clinical T category. However, it was revised to the solid portion size based on study results showing that the solid portion size was more closely associated with patients' prognosis than the total tumor size was [10,26–28]. At present, in the circumstances where the solid portion size has a direct association with SUVmax [13–15], there should be doubt regarding whether the SUVmax of the primary tumor could contribute to the preoperative evaluation of lung adenocarcinomas. However, the results of our study demonstrated that SUVmax, as either a continuous or a categorical variable, could act as an independent prognostic factor in the revised staging system. The addition of the proposed $_{PET}$T category significantly improved prognostication, and it was a useful parameter for the reclassification of the tumors. Thus, we cautiously suggest that the proposed $_{PET}$T category could be integrated in the current lung cancer staging system, and it could be used as a nonanatomical element in prognostication beyond the conventional TNM classification [12].

A plausible explanation of the significance of SUVmax (or $_{PET}$T category) along with the solid portion size-based T categorization is its association with subtypes of adenocarcinomas [29,30]. According to Nakamura et al. [30], SUVmax values were the highest in micropapillary predominant adenocarcinomas, followed by solid predominant, invasive mucinous, acinar predominant, papillary predominant, and lepidic predominant adenocarcinomas. Recent studies showed that patients with micropapillary or solid predominant adenocarcinomas had significantly poorer survival [31–33]. Therefore, the integration of SUVmax in the current staging system may enable subdividing adenocarcinomas in the same clinical T category according to their inherent biological characteristics.

Pathologic upstaging or downstaging is a common finding in NSCLCs [34], and it is associated with an inferior survival rate [35]. In this context, the $_{PET}$T category may play a role as a useful stage-shifting parameter prior to the surgery, and it could improve the accuracy of risk stratification and subsequent treatment planning. For example, adjuvant chemotherapy may be offered in resected stage IB patients with $_{PET}$T3. In addition, sublobar resection may be performed in stage IA1 with $_{PET}$T1 given the fact that the increased distinction between $cT_{Modified}$1a and $cT_{Modified}$1b was achieved by using $_{PET}$T. These

potential suggestions need to be investigated in the future prospective cohort studies.

An important issue in the categorization of a continuous variable is determining the cutoffs, which also applies to SUVmax. We used quartile values for the trichotomization of SUVmax. Optimal thresholds based on P-values determined by statistical tests (i.e., the minimum P-value approach) were not adopted because they could have diminished the generalizability of the study's results and overestimated the prognostic performance [23]. Nevertheless, to improve prognostic stratification, cutoffs should be established in the training cohort and validated externally. Thus, a larger prospective cohort is needed to confirm our findings and to explore optimal SUVmax thresholds.

There are several limitations of this study. First, our study was performed retrospectively at a single center. Second, an a priori sample size estimation was not conducted. However, a large number of early stage lung adenocarcinomas were collected and analyzed. Third, adenocarcinoma subtypes were not analyzed in our study. The purpose of our study was to reveal prognostic factors that are useful in clinical staging. Therefore, only variables that could be obtained preoperatively were included in the Cox models. Fourth, because long-term survival data were not investigated in our study population, the analysis of overall survival was limited. However, because overall survival would be helpful in appropriately evaluating staging variables, further validation studies are warranted.

5. Conclusions

We conclude that SUVmax is an independent prognostic factor after adjustment for the clinical T category for surgically treated adenocarcinomas. The proposed $_{PET}$T category could be utilized as a complementary nonanatomical T factor in preoperative prognostic grouping and stage adjusting.

Declaration of Competing Interest

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Transparency document

The Transparency document associated with this article can be found in the online version.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.06.013.

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