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Clinically simplified screening methods to evaluate maximum standard uptake value from F-18-FDG-PET/CT in patients with non-small-cell lung cancer

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Abstract

Maximum standard uptake value (SUVmax) of F-18-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) is reportedly useful for evaluating regional lymph nodes (RLNs) of non-small-cell lung cancer (NSCLC) to predict malignancy. However, it is difficult for clinicians to measure SUVmax (mSUVmax) as calculated by a workstation.

We assessed the utility of simplified SUVmax (sSUVmax) in screening RLNs for pathologic malignancy. The highest color was visually defined in the region of interest. The resulting color can be quantified using the color bar, and interpreted as sSUVmax. Patients in respiratory medicine and surgery who underwent both contrast-enhanced CT and FDG-PET/CT within 3 months before radical lobectomy were evaluated retrospectively. The correlation was examined by regression analysis and receiver operating characteristic (ROC) curve analyses.

Participants comprised 69 patients with NSCLC treated between May 2009 and April 2016. Medical group comprised 22 patients from respiratory medicine. The prediction model could be written as a linear relationship (mSUVmax = $1.019 \times$ sSUVmax; $R^2 = 0.930$). A total of 316 RLNs resected by surgery in total cohort were pathologically determined. From ROC curves, area under curve for sSUVmax was 0.72 (95% confidence interval, 0.61–0.83; $P < .0002$). The cutoff sSUVmax was 2.42 (sensitivity, 52%; specificity, 88%; accuracy, 85%).

The sSUVmax allows quantification of colors from FDG-PET/CT and shows a close correlation to mSUVmax. This value may have potential in screening for RLNs, and thoracic clinicians can readily determine the value. These findings may facilitate better planning of therapeutic strategy in the real world.

Abbreviations: AUC = area under the curve, CI = confidence interval, CT = computed tomography, DTPI = dual time point PET imaging, FDG-PET/CT = integrated F-18-fluorodeoxyglucose positron emission tomography-computed tomography, mSUVmax = measured SUVmax, NSCLC = non-small-cell lung cancer, pSUVmax = predicted SUVmax, R^2 = coefficient of determination, RLN = regional lymph node, ROC = receiver operating characteristic, ROI = region of interest, sCT = short-axis diameter of regional lymph nodes from contrast-enhanced CT, sSUVmax = simplified SUVmax, SUV = standardized uptake value, SUVmax = maximum SUV.

Keywords: color scale, F-18-fluorodeoxyglucose positron emission tomography-computed tomography, lung cancer, simplified maximum standard uptake value

1. Introduction

Integrated F-18-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) has become widely used in clinical practice and provides important information for staging patients with non-small-cell lung cancer (NSCLC).[1] The principle in lung cancer has been to determine nodal status based on the anatomical location (station or zone) of the metastatic lymph node, rather than on the number of metastatic lymph nodes.[2] Metastases to regional lymph nodes (RLNs) have been diagnosed using size criteria, mainly from contrast-enhanced CT, even though the sensitivity and specificity of this modality are limited. In the 8th edition of the primary tumor lymph node metastases (TNM) staging system, FDG-PET/CT was not given a major role in the staging of lymph nodes because metastatic nodes are not clearly separable for accurate counting on the resulting images.[2] Some reports, even from tuberculosis-endemic countries, have suggested that FDG-PET/CT could allow more accurate staging of RLNs than CT.[3–5] To improve diagnostic accuracy, thoracic clinicians such as respiratory oncologists and thoracic surgeons have considered simultaneous evaluation with FDG-PET/CT and contrast-enhanced CT[6], and radiologists specializing in nuclear medicine have investigated methods such as dual time point PET imaging (DTPI), DTPI with a retention index, and visual analysis.[3–5,7] The clinical practical guidelines in NSCLC also described FDG-PET/CT as more sensitive than CT in identifying RLNs.[8] The FDG-PET/CT has been shown to be useful in restaging after adjuvant therapy. Thoracic clinicians wish to take into consideration the practical use of FDG-PET/CT on diagnosis, practical therapeutic plan, and prediction on

prognosis. Although investigators reported more accurate and sensitive methods, clinicians need simple methods which had clinical practical evidence as much as possible. The standardized uptake value (SUV) has been studies for diagnostic utilization,[9] prognostic factor after surgical treatment,[10] radiotherapy,[11] and treatments of NSCLC.[12]

Three types of SUV are currently used to evaluate solitary pulmonary nodules: maximum SUV (SUVmax); mean SUV of a region of interest (ROI); and mean SUV over the full tumor volume. SUVmax reportedly provides the highest diagnostic accuracy for solitary pulmonary nodules among these various semi-quantitative approaches.[13] Visual interpretation has been used from the beginning of PET evaluation and plays an important role in diagnosis from FDG-PET/CT. Recent studies have reported that the accuracy of semi-quantitative SUV analyses is no better than that of visual analysis.[4,7] Here we propose a "simplified SUVmax" (sSUVmax) using a color spectrum bar. The investigator determines the color highest in the ROI, and this is then easily quantified using the color bar as the sSUVmax. With sSUVmax, a combination of visual interpretation and semi-quantitative SUV analyses is provided.

Given these backgrounds, when we use FDG-PET/CT for staging patients with NSCLC, the sSUVmax of RLNs is determined according to the anatomical location of the lymph node. In study I, the aim was to clarify the correlation between sSUVmax and measured SUVmax (mSUVmax) as calculated by a workstation. The aim of study II was to determine whether sSUVmax could be clinically applicable by screening RLNs for pathologic malignancy as the validation study.

2. Methods

2.1. Patients

A retrospective analysis was performed using data from patients who had undergone both contrast-enhanced CT of the chest and FDG PET/CT within 3 months before lobectomy with RLN

dissection, representing "radical lobectomy." Patient information was obtained from the databases of the Department of Respiratory Medicine and the Department of General Thoracic Surgery at the National Center for Global Health and Medicine, Tokyo, Japan.

Information from the database of the Department of Respiratory Medicine as the "Medical group" was used in study I as a training set (Fig. 1A). Thirty-one patients underwent both contrast-enhanced CT and FDG PET/CT imaging within 3 months before radical lobectomy during this period. Nine patients were excluded because PET imaging data had not been archived in a workstation in the Department of Nuclear Medicine. Both mSUVmax and sSUVmax were able to be evaluated from FDG PET/CT for 22 patients in the medical group.

A total of 212 patients with NSCLC underwent surgical treatment in the Department of General Thoracic Surgery between January 2013 and December 2015. Of these, 72 patients were excluded because they had undergone either limited resection or lymph node systematic sampling. Fifty-six of the remaining 140 patients underwent both contrast-enhanced CT and FDG PET/CT within 3 months before radical lobectomy during this period as the surgical group. Nine patients in the medical group overlapped with patients in the surgical group. The remaining 13 patients in the medical group and 56 patients in the surgical group were combined as the total group in study II for use as a validation set.

2.2. Ethical considerations

This study was conducted according to the principles of the Declaration of Helsinki. The study protocol was approved by our institutional ethics committee (NCGM-G-002237-00).

2.3. PET/CT and diagnostic CT

All patients fasted for ≥6 hours before blood glucose level was measured and FDG was intravenously administered (dose range, 185–370 MBq). Sixty minutes after injecting FDG, low-dose CT
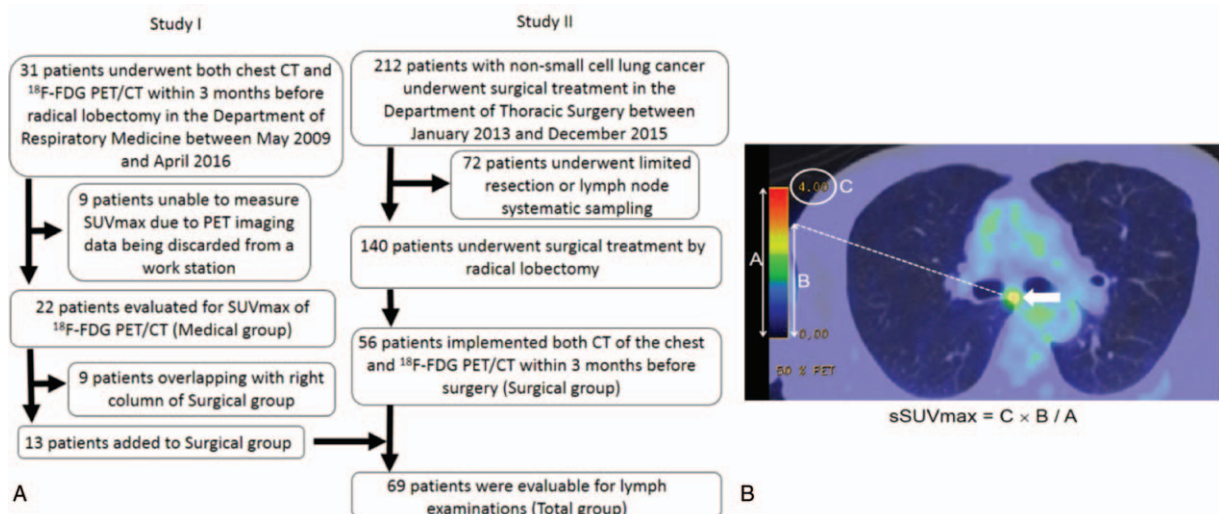

Figure 1. (A) Study flowchart. (B) Method for calculating simplified SUVmax (sSUVmax) using a color spectrum. On the color bar, a lower SUV of black or dark blue equals zero and a higher value of red is equal to "C" in this study. The color in the spectrum corresponding to the target lesion is decided on PET/CT imaging, then a score is given according to the color bar. We measure the distance from the bottom of the color bar to mark B. We also measure the distance from the bottom to C, as the full length A of the color bar. The sSUVmax is calculated using the following formula: sSUVmax = C × B/A. CT = computed tomography, F-18-FDG PET/CT = F-18-fluorodeoxyglucose positron emission tomography-computed tomography, radical lobectomy = lobectomy with systematic nodal dissection, SUV = standardized uptake value, SUVmax = maximum SUV value in region of interest.

was performed and used for attenuation correction and image fusion. Emission images were acquired in 3-dimensional mode for 2.5 min/bed position to obtain an image from the skull vertex to the upper thighs. All examinations were performed using a PET/CT system (Biograph biograph 16; Siemens, Munich, Germany). PET data were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (3 iterations, 8 subsets). For semi-quantitation, SUVmax in each ROI (mSUVmax) was calculated using an image workstation (Syngo.via; Siemens) by a radiologist specializing in nuclear medicine and a resident in respiratory oncology. Contrast-enhanced CT was performed using either a Toshiba Aquilion ONE (Toshiba Medical System Co Ltd, Tochigi, Japan), SOMATOM Definition Flash (Siemens Healthineers Japan Co Ltd, Tokyo, Japan), or GE Discovery CT750HD (GE Healthcare/ Japan Co Ltd, Hino, Japan), with image reconstruction performed using a slice thickness of 1 or 5 mm. Contrast enhancement was used in all CT studies. Typically, 100 mL of contrast medium was administered to the patient at a rate of 2.0 to 2.5 mL/s, and scan delay was 50 seconds. Acquisition parameters were as follows: tube load, 250 to 350 mAs; tube voltage, 120 kVp.

2.4. sSUVmax and other imaging evaluations

We used both CT and PET/CT images distributed from the Picture Archiving and Communication System of our hospital. Examined lesions were those resected under radical lobectomy; that is, the primary lesion and dissected RLNs. In the case of contrast-enhanced CT, short-axis diameter was also measured for all dissected RLNs. The primary lesion and all dissected RLNs were evaluated directly for sSUVmax and mSUVmax. When lesions were not clearly separated for accurate counting on PET images, SUV was determined depending on the anatomical location (station or zone) of the lymph node on both CT and PET/ CT. On the color spectrum bar, the lowest (black or dark blue) value for SUV was considered as zero, while the highest (red) value was termed "C" in this study. Radiologists specializing in nuclear medicine set the color bar to recognize the gradations at each lesion and set the C-value as the saturation point for F-18-FDG uptake on an image workstation. Each sSUVmax was determined as shown in Figure 1B. First, the color of the target lesion was taken as the highest color within the ROI of the dissected lymph nodes or primary tumor. Second, this color was marked on the color bar. Third, the distance from the bottom of the color bar to the mark was measured as value B. The distance from the bottom of the color bar to C on the color bar was value A. The sSUVmax was calculated using the following formula: $sSUVmax = C \times B/A$.

We measured the highest SUV to analyze mSUVmax using software on a workstation for PET imaging. On regression analysis, the high value for mSUVmax beyond the upper value on each color bar was set as the value of C.

2.5. Image evaluation

In the medical group, 3 thoracic clinicians independently determined both the sSUVmax from PET images and short-axis diameter of RLNs from contrast-enhanced CT (sCT). Mean values for sSUVmax and sCT were then calculated. Each mSUVmax was independently determined by 1 clinician and 1 specialist in nuclear medicine, with the final decision made by consensus. Mean values for mSUVmax were also calculated. In

the surgical group, 1 thoracic clinician determined both sSUVmax and sCT. Evaluations of sSUVmax, mSUVmax, and sCT were obtained in a blinded manner from pathologic results.

2.6. Analytical and statistical methods

Sensitivity, specificity, positive likelihood ratio, and accuracy were calculated using standard definitions.[14] The relationship between sSUVmax and mSUVmax was analyzed by linear regression analysis using SPSS Statistics version 22 software (IBM Japan Ltd, Tokyo, Japan) and Stata version 14 software (Stata Corp LP, College Station, TX). Receiver operating characteristic (ROC) curve analyses were generated using SigmaPlot version 13 software (Systat Software, Inc, San Jose, CA) and Stata version 14 software. Cronbach alpha values were analyzed for inter- and intraobserver reproducibility by SPSS Statistics version 22 software. A $P < .05$ was considered to indicate a statistically significant outcome.

3. Results

3.1. Patients

Twenty-two patients were evaluated in study I as a training group, and 69 patients were included in study II as a validation set (Fig. 1A).

Table 1 shows the background characteristics of each group. The total group comprised 69 patients (46 men, 23 women) with a median age of 72 years (range, 46–86 years). The underlying pathology was adenocarcinoma in 47 patients, squamous cell carcinoma in 16, large cell carcinoma in 3, and adenosquamous cell carcinoma in 1. All patients underwent radical lobectomy or

Table 1

Background characteristics.

	Medical group	Surgical group	Total group
Number in group	22	56	69
Gender			
Male/female, n	15/7	37/19	46/23
Age			
Median (range), y	70 (58–83)	72 (46–86)	72 (46–86)
Smoking			
Current/past/never/unknown	6/10/5/1	18/24/12/2	23/29/14/3
Diabetes, +/−	5/17	13/43	15/54
Histologic diagnosis			
Adenocarcinoma	12	39	47
Squamous cell	7	13	16
Large cell	2	2	3
Adenosquamous	1	0	1
Undifferentiated	0	1	1
Other (adenoid cystic)	0	1	1
Primary			
RU/RM/RL/LU/LL	6/2/2/7/4	15/5/8/19/9	17/6/9/25/11
RU + RL	1	0	1
Operation			
rU/rM/rL/rM + rL/lU/lL	7/1/2/1/7/4	15/5/6/1/19/9	19/5/6/2/26/10
Right pneumonectomy	0	1	1
ND2a/ND2a-1/ND2a-2	2/6/14	1/22/33	3/25/41
Pathologic stage (TNM version 7)			
p-T: Tis/T1a/T1b/T2a/T2b/T3	0/3/5/9/3/2	1/17/ 6/23/4/5	1/17/11/28/5/7
p-N: N0/N1/N2	16/3/3	42/5/9	50/7/12

LL = left lower lobe, IL = left lower lobectomy, LU = left upper lobe, lU = left upper lobectomy, ND = lymph node dissection, RL = right lower lobe, rL = right lower lobectomy, RM = right middle lobe, rM = right middle lobectomy, RU = right upper lobe, rU = right upper lobectomy, TNM = tumor lymph node metastases.

Pathologic findings by resected lesions and each SUV value by PET-CT in medical group.

	Subtotal	Pathologic evaluation		sSUVmax, median (IQR)	pSUVmax, median (IQR)	mSUVmax, median (IQR)	sCT, mm/ median, (IQR)
Nodal station							
N1	47	Positive	3	1.15 (0–4.07)	1.17 (0–4.14)	1.95 (0.34–3.80)	4.60 (1.43–5.17)
		Negative	44	1.35 (0.68–2.44)	1.37 (0.69–2.49)	1.94 (1.42–2.53)	4.47 (3.25–6.68)
N2	67	Positive	7	2.43 (1.57–2.77)	2.48 (1.60–2.82)	2.31 (2.13–2.96)	8.80 (4.60–10.9)
		Negative	60	1.30 (0.49–1.96)	1.32 (0.50–2.0)	1.16 (0.50–2.26)	4.40 (3.48–6.02)
N1 + N2	114	Positive	10	2.22 (0.96–3.08)	2.26 (0.98–3.13)	2.27 (1.61–3.17)	6.03 (4.42–10.9)
		Negative	104	1.33 (0.56–2.12)	1.36 (0.57–2.16)	1.84 (0.64–2.33)	4.40 (3.41–6.50)
Primary lesions	22	Positive	22	4.0 (3.98–4.02)	4.08 (4.06–4.10)	4.0 (3.98–4.02)	–
Total lesions	136	Positive	32	3.99 (2.03–4.0)	4.07 (2.07–4.08)	3.99 (2.16–4.0)	–
		Negative	104	1.33 (0.56–2.12)	1.36 (0.57–2.16)	1.84 (0.64–2.33)	–

IQR = interquartile range (25% to 75% IQR), mSUVmax = measured SUVmax by an image workstation, N1 = ipsilateral peribronchial, interlobar, or hilar node involvement, N2 = ipsilateral mediastinal node involvement, pSUVmax = predicted SUVmax, sCT = short-axis diameter of regional lymph nodes from computed tomography, sSUVmax = simplified SUVmax, SUV = standardized uptake value, SUVmax = maximum SUV value in region of interest.

pneumonectomy. Pathologic T categories of TNM classification (version 7) were Tis in 1 patient, T1a in 17, T1b in 11, T2a in 28, T2b in 5, and T3 in 7. Pathologic N categories were N0 in 50, N1 in 7, and N2 in 12.

3.2. Study I: training set using the medical group

Table 2 shows the number of pathologically proven lesions resected by surgical treatment in the medical group. A total of 136 lesions were pathologically evaluated. Of these, 32 were pathologically positive for malignancy and 104 were negative. Each lesion was examined simultaneously using the 3 methods of sSUVmax, mSUVmax, and sCT. Median sSUVmax value was 3.99 in lesions with involvement and 1.33 in lesions without involvement. Median mSUVmax value was 3.99 in lesions with involvement and 1.84 in lesions without involvement. Figure 2A

shows the linear regression model without constant. The approximate equation between mSUVmax (y-axis) and sSUVmax (x-axis) could be expressed as y = 1.019x, with 0 as the intercept and 1.019 (95% confidence interval [CI]: 0.97–1.07) as the slope. The coefficient of determination (R^2) was 0.93 with a P-value <.0001. Using this equation, predicted SUVmax (pSUVmax) was estimated from the sSUVmax. Figure 2B shows the ROC curves for sSUVmax, pSUVmax, and mSUVmax. Because the slope of the approximate equation was nearly 1, ROC curves were superimposed between sSUVmax and pSUVmax. The area under the cures (AUCs) of ROC curves for sSUVmax, pSUVmax, and mSUVmax were 0.82 (95% CI: 0.72–0.92), 0.82 (95% CI: 0.72–0.92), and 0.82 (95% CI: 0.72–0.92), with P < .0001 for significant differences from 0.5 in each case. The results of comparison between sSUVmax and mSUVmax were not significant using the Bonferroni test (P = .84).
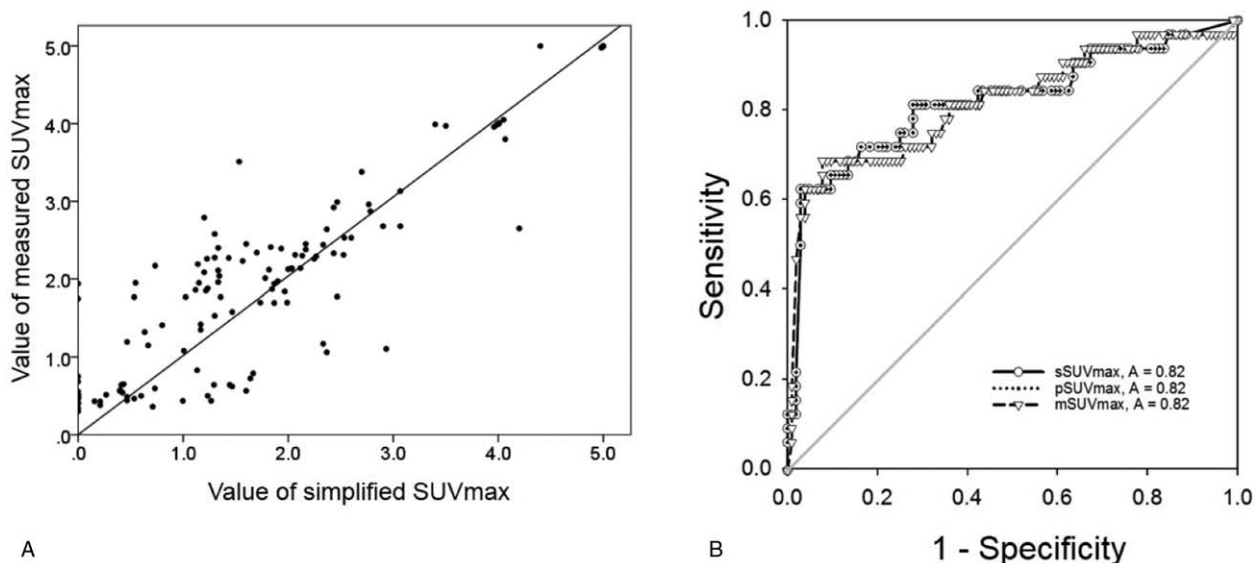

Figure 2. (A) Linear regression analysis between simplified SUVmax (sSUVmax) and measured SUVmax (mSUVmax). The linear regression equation without constant coefficient was estimated as following formula with the corresponding P < .00001: mSUVmax = 1.019 × sSUVmax. R^2 is 0.929, indicating that about 93% of mSUVmax can be accounted for by sSUVmax. (B) Receiver operating characteristic (ROC) curves for simplified SUVmax (sSUVmax), predicted SUVmax (pSUVmax), and measured SUVmax (mSUVmax) for regional lymph nodes with the primary tumor in the medical group. Solid line with open circle indicates sSUVmax, dotted line with crosshair indicates pSUVmax, and medium dashed line with triangle indicates mSUVmax. A, area under the ROC curve. No significant differences in sensitivity, specificity, positive likelihood ratio, or accuracy were seen between sSUVmax and pSUVmax according to the Bonferroni test (P = 1.0), or between sSUVmax and mSUVmax (P = .84), and between pSUVmax and mSUVmax (P = .84), respectively.

Table 3

Pathologic findings by resected lesions and each SUV value by PET-CT in total group.

	Subtotal	Pathologic evaluation		sSUVmax, median (IQR)	pSUVmax, median (IQR)	sCT, mm/median (IQR)
Nodal station						
N1	128	Positive	8	2.50 (0.43–3.95)	2.55 (0.43–4.02)	4.40 (1.43–6.20)
		Negative	120	1.52 (1.20–2.19)	1.55 (1.22–2.23)	4.10 (3.05–5.40)
N2	188	Positive	19	2.43 (1.56–2.80)	2.48 (1.60–2.85)	7.30 (5.40–9.10)
		Negative	169	1.50 (0–1.90)	1.53 (0–1.94)	4.10 (3.10–5.10)
N1 + N2	316	Positive	27	2.43 (1.57–3.60)	2.48 (1.60–3.67)	6.10 (4.83–8.83)
		Negative	289	1.50 (0.34–2.0)	1.53 (0.34–2.04)	4.10 (3.10–5.30)
Primary lesions	69	Positive	69	4 (2.85–5)	4.08 (2.90–5.09)	–
Total lesions	385	Positive	96	4.0 (2.13–5.0)	4.08 (2.16–5.09)	–
		Negative	289	1.50 (0.34–2.0)	1.53 (0.34–2.04)	–

IQR = interquartile range (25% to 75% IQR), mSUVmax = measured SUVmax by an image workstation, N1 = ipsilateral peribronchial, interlobar, or hilar node involvement, N2 = ipsilateral mediastinal node involvement, pSUVmax = predicted SUVmax, sCT = short-axis diameter of regional lymph nodes from computed tomograpy, sSUVmax = simplified SUVmax, SUV = standardized uptake value, SUVmax = maximum SUV value in region of interest.

Cronbach alpha was evaluated for inter-observer reproducibility among 3 thoracic clinicians. The alpha coefficient was 0.979. Intra-observer reproducibility was also examined by Cronbach alpha among 2 thoracic clinicians. The alpha coefficient was 0.914 for the first clinician and 0.999 for the second clinician.

3.3. Study II: validation set study using total group

Table 3 shows numbers of pathologically confirmed lymph nodes according to pathologic N categories in the total group. In total, 316 lymph nodes were pathologically evaluated, revealing 27 nodes pathologically positive for malignancy and 289 nodes negative. Each lesion was examined simultaneously using the methods of sSUVmax and sCT. On the nodal station of N1 and N2, median sSUVmax value was 2.43 with involvement and 1.50 without involvement. Median CT value was 6.1 mm with involvement and 4.1 mm without involvement. Figure 3A shows the ROC curves for sSUVmax, pSUVmax, and sCT. The ROC curves were also superimposed between sSUVmax and pSUV-max. No significant difference in ROC curve areas was seen between sSUVmax and pSUVmax according to the Bonferroni test ($P = 1.0$). The AUC was 0.72 (95% CI: 0.61–0.83, $P = .0001$) for sSUVmax and 0.72 (95% CI: 0.61–0.83, $P = .0001$) for pSUVmax. The AUC for sCT was 0.74 (95% CI: 0.64–0.85, $P < .0001$), slightly better than the AUCs for the other values. Optimal cutoffs for sSUVmax, pSUVmax, and sCT to predict metastatic lymph nodes were ≥2.42 (52% sensitivity, 88% specificity), ≥2.46 (52% sensitivity, 88% specificity), and ≥4.88 mm (77% sensitivity, 67% specificity) (Fig. 3B). In an additional study, predicting metastatic lymph nodes by FDG-PET/CT imaging combined with contrast-enhanced CT, all evaluation methods were improved (Table 4). Accuracy improved from 67.6% for sCT alone to 87.6% for sCT combined with sSUVmax or pSUVmax from PET.

4. Discussion

The mSUVmax on FDG-PET/CT of lung mass or of RLNs has been shown to correlate to the pathology.[15] However,
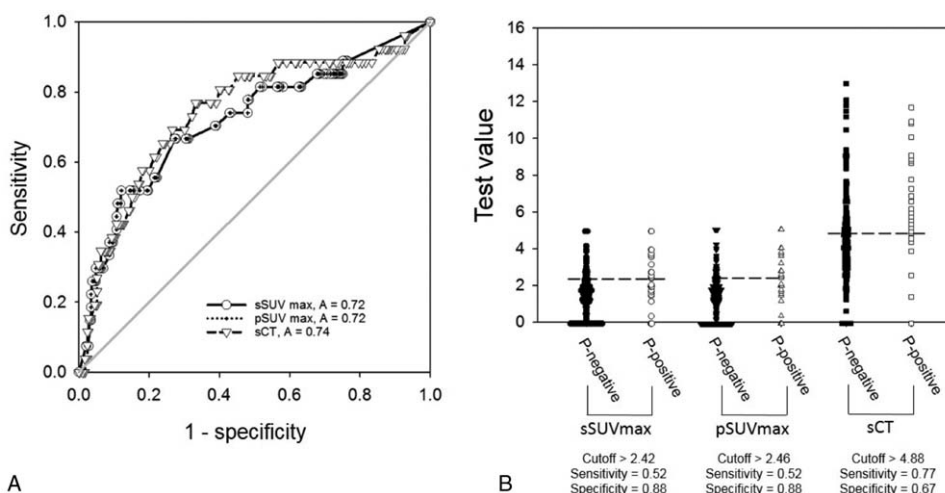

Figure 3. Receiver operating characteristic (ROC) curves and dot histograms for simplified SUVmax (sSUVmax) and predicted SUVmax (pSUVmax) of regional lymph nodes. (A) Receiver operating characteristic curves. Solid line with open circle indicates sSUVmax, dotted line with crosshair indicates pSUVmax, and medium dashed line with triangle indicates short axis of lymph node on computed tomography (sCT). A, area under the ROC curve. No significant difference in ROC curve areas was seen between sSUVmax and pSUVmax according to the Bonferroni test ($P = 1.0$). (B) Dot histograms. Closed circle indicates sSUVmax with pathologically negative metastases of each lymph node (P-negative). Open circle is sSUVmax with pathologic positive metastases of each lymph node (P-positive). Closed triangle indicates pSUVmax with P-negative, open triangle indicates pSUVmax with P-positive. Closed square represents sCT with P-negative, and open square represents sCT with P-positive. The dashed line indicates the optimal cutoff for each examination.

Table 4

Evaluation of regional lymph node metastases by each method (lymph nodes, n=316).

	Sensitivity, %	Specificity, %	Positive likelihood ratio	Accuracy, %
Single method				
sSUVmax	51.9	87.9	4.28	84.8
pSUVmax	51.9	87.9	4.28	84.8
sCT	76.9	66.8	2.32	67.6
Combined methods				
sSUVmax + sCT	42.3	91.7	5.10	87.6
pSUVmax + sCT	42.3	91.7	5.10	87.6

No significant differences in sensitivity, specificity, positive likelihood ratio, or accuracy were seen between sSUVmax and pSUVmax according to the Bonferroni test ($P=1.0$).
CT = computed tomography, pSUVmax = predicted SUVmax, sCT = short-axis diameter of regional lymph nodes from computed tomography, SUVmax = maximum standardized uptake value, sSUVmax = simplified SUVmax.

mSUVmax is a precise analysis and sometimes needs access to the workstation of a PET/CT imaging master program in the Division of Nuclear Medicine. Thoracic clinicians need more simplified access and easier indicators to decide on therapeutic strategies and to monitor imaging findings. The purpose of the sSUVmax, as proposed in this study, was to allow easy quantification of the color resulting from imaging as a finite number. A close correlation was identified between sSUVmax and mSUVmax, and sSUVmax was estimated from mSUVmax by the approximate equation with a slope of about 1 and an intercept of 0. As a result, if the color bar was set appropriately, sSUVmax was considered almost equivalent to mSUVmax. sSUVmax can thus provide thoracic clinicians with easy evaluation of RLNs comparable to the ideal measurement of mSUVmax. C-value was considered able to be set at any point within the linear gradation range of the color bar. In this study, C-value was set at the saturation point of F-18-FDG uptake to calculate the SUV value as exactly as possible. If C-value is set lower than the saturation point, distance A will be shorter, but the proportion of C to A would remain unchanged. Among primary lesions that did not show saturated F-18-FDG uptake in the medical group, no significant difference was evident between sSUVmax and mSUVmax by Wilcoxon nonparametric testing ($P=.715$). The sSUVmax will not change unless mSUVmax changes.

The strengths of sSUVmax in this present study are that thoracic clinicians can easily calculate the value from image data on general terminal computers distributed in the Division of Nuclear Medicine, at any time, in any part of the hospital and any number of times. Our validation demonstrated that sSUVmax is useful for screening RLNs for pathologic malignancy, performing as well as mSUVmax, the established parameter in this setting. Even in a real-world setting, an sSUVmax of RLNs >2.42 achieved 84.5% accuracy, similar to previous reports of mSUVmax.[15,16] When sSUVmax was combined with sCT, diagnostic accuracy improved to 87.6%, again similar to a previous report of mSUVmax with sCT.[6]

Several limitations to the present study must be considered when interpreting our results. First, because this was a retrospective analysis, the analyzed data included some biases. A prospective study to confirm our findings is thus warranted. Second, the prevalence of performing both contrast-enhanced CT and FDG PET/CT before radical lobectomy was considered low. Because all patients were treated by radical lobectomy and had tumors at a relatively early stage, carcinoma progression was generally slow. The allowable interval was thus relatively wide in this study. In our data set, 61% of patients in the total group underwent both examinations within 1 month before surgery, and 11% within 3 months. This interval should ideally be as short as possible. Third, specialists in nuclear medicine should set an appropriate C-value in color bar and PET image to recognize the SUVmax within each ROI. These specialists played an important role in this evaluation. Some reports have described visual scales used for interpreting lymph nodes on PET.[4,7,9] Interpretation of lesions on PET has been determined visually until now. Some recent reports have described the accuracy of visual evaluation as similar or superior to semi-quantitative SUV methods or DTPI.[4,7] As sSUVmax is considered a combination of visual interpretation and semi-quantitative SUV analyses, once visual analysis has been quantified, the results would be easily combined with sCT or any other method. Fourth, limit of this approach seemed to be the potential variability and poor reproducibility of this new parameter. Cronbach alpha coefficient for inter-observer variability was 0.979, which was considered desirable. The alpha coefficient for intra-observer variability was 0.914 to 0.999, which was considered "tolerated" to "desirable". Although the sSUVmax value obtained using the color bar correlated closely with mSUVmax and could play a new role in the evaluation of patients with NSCLC, this parameter should not be adopted in place of mSUVmax until further studies can evaluate and validate the clinical utility, reproducibility, and feasibility of sSUVmax.

In conclusion, sSUVmax allows quantification of a color into a finite value and shows a close relationship to mSUVmax. When the color bar is set appropriately, sSUVmax appears almost equivalent to mSUVmax. This sSUVmax is also thought to combine semi-quantitative SUV analyses with visual interpretation. As a result, sSUVmax may offer a good parameter for screening RLNs and could be applicable to other pathologies investigated using mSUVmax. Thoracic clinicians can perform this evaluation easily at any time in any part of the hospital in real-world settings.

Author contributions

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References

 [1] Lardinois D, Weder W, Hany TF, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 2003;348:2500–7.
 [2] Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. J Thorac Oncol 2015;10:1675–84.
 [3] Kim YK, Lee KS, Kim BT, et al. Mediastinal nodal staging of nonsmall cell lung cancer using integrated 18F-FDG PET/CT in a tuberculosis-endemic country: diagnostic efficacy in 674 patients. Cancer 2007; 109:1068–77.
 [4] Yen RF, Chen KC, Lee JM, et al. 18F-FDG PET for the lymph node staging of non-small cell lung cancer in a tuberculosis-endemic country: is dual time point imaging worth the effort? Eur J Nucl Med Mol Imaging 2008;35:1305–15.
 [5] Lee JW, Kim BS, Lee DS, et al. 18F-FDG PET/CT in mediastinal lymph node staging of non-small-cell lung cancer in a tuberculosis-endemic country: consideration of lymph node calcification and distribution pattern to improve specificity. Eur J Nucl Med Mol Imaging 2009; 36:1794–802.
 [6] Kubota K, Murakami K, Inoue T, et al. Additional value of FDG-PET to contrast enhanced-computed tomography (CT) for the diagnosis of mediastinal lymph node metastasis in non-small cell lung cancer: a Japanese multicenter clinical study. Ann Nucl Med 2011;25:777–86.
 [7] Rogasch JM, Steffen IG, Riedel S, et al. Dual time point imaging for F18-FDG-PET/CT does not improve the accuracy of nodal staging in non-small cell lung cancer patients. Eur Radiol 2016;26:2808–18.
 [8] National Comprehensive Cancer Network. Clinical practical guidelines in oncology, non-small cell lung cancer NCCN.org Version 2.2018.
Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed December 19, 2017.
 [9] Vansteenkiste JF, Stroobants SG, De Leyn PR, et al. Lymph node staging in non-small-cell lung cancer with FDG-PET scan: a prospective study on 690 lymph node stations from 68 patients. J Clin Oncol 1998;16:2142–9.
[10] Berghmans T, Dusart M, Paesmans M, et al. Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. J Thorac Oncol 2008;3:6–12.
[11] Na F, Wang J, Li C, et al. Primary tumor standardized uptake value measured on F18-fluorodeoxyglucose positron emission tomography is of prediction value for survival and local control in non-small-cell lung cancer receiving radiotherapy: meta-analysis. J Thorac Oncol 2014; 9:834–42.
[12] Paesmans M, Berghmans T, Dusart M, et al. Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer: update of a systematic review and meta-analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. J Thorac Oncol 2010;5:612–9.
[13] Degirmenci B, Wilson D, Laymon CM, et al. Standardized uptake value-based evaluations of solitary pulmonary nodules using F-18 fluorodeox-yglucose-PET/computed tomography. Nucl Med Commun 2008;29:614–22.
[14] Newman TB, Browner WS, Cummings SR. Stephen SB, Cummings SR, Browner WS, Grady D, Hearst N, Newman TB. Desirning studies of medical tests. Designing Clinical Research 2nd edLippincott Williams & Wilkins, Philadelphia, PA:2001;175–93.
[15] Bryant AS, Cerfolio RJ, Klemm KM, et al. Maximum standard uptake value of mediastinal lymph nodes on integrated FDG-PET-CT predicts pathology in patients with non-small cell lung cancer. Ann Thorac Surg 2006;82:417–23.
[16] Cerfolio RJ, Ojha B, Bryant AS, et al. The role of FDG-PET scan in staging patients with nonsmall cell carcinoma. Ann Thorac Surg 2003; 76:861–6.