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New PET/CT criterion for predicting lymph node metastasis in resectable advanced (stage IB-III) lung cancer: The standard uptake values ratio of ipsilateral/contralateral hilar nodes

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Abstract

Background: The aim of the present study was to use surgical and histological results to develop a simple noninvasive technique to improve nodal staging using preoperative PET/CT in patients with resectable lung cancer.

Methods: Preoperative PET/CT findings (pStage IB–III 182 patients) and pathological diagnoses after surgical resection were evaluated. Using PET/CT images to determine the standardized uptake value (SUV) ratio, the SUV_{max} of a contralateral hilar lymph node (on the side of the chest opposite to the primary tumor) was measured simultaneously. The I/C-SUV ratio was calculated as ipsilateral hilar node SUV/contralateral hilar node SUV. Receiver operating characteristic (ROC) curves were then used to analyze those data.

Results: Based on ROC analyses, the cutoff I/C-SUV ratio for diagnosis of lymph node metastasis was 1.34. With a tumor ipsilateral lymph node $SUV_{max} \geq 2.5$, an IC-SUV ratio ≥ 1.34 had the highest accuracy for predicting N1/N2 metastasis; the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of nodal staging were 60.66, 85.11, 84.09, 62.5 and 71.29%, respectively.

Conclusions: When diagnosing nodal stage, a lymph node I/C-SUV ratio ≥ 1.34 can be an effective criterion for determining surgical indications in advanced lung cancer.

KEYWORDS
computed tomography, lung cancer, lymph node, metastasis, positron-emission tomography

INTRODUCTION

Accurate nodal staging, including ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), is crucial for determining optimal treatment strategies and optimizing prognoses in lung cancer. Although surgical resection for early-stage lung cancer is associated with favorable prognoses, the prognoses for N1 and N2 disease unfortunately remain unsatisfactory.[1–5]

Although mediastinoscopy is the gold standard, PET/CT, a noninvasive imaging method that integrates the malignant functional information provided by PET with anatomic information provided by CT, is being increasingly used for nodal staging. As a general rule, a maximum standardized uptake value (SUV_{max}) of ≥ 2.5 is indicative of a malignant tumor or lymph node.[6–9] In studies in which a node $SUV_{max} \geq 2.5$ on PET/CT was the sole criterion for detection of metastatic lymph nodes, the sensitivity and specificity estimates for this threshold were 81.3% (95% confidence intervals [CI] 70.2–88.9) and 79.4% (95% CI: 70–86.5), respectively.[9] However, in older lung cancer patients, thoracic lymph nodes enlarged due to inflammation also show increased FDG uptake. In addition, sublobar resection is considered the optimal approach for selected patients with small (diameter:

≤2 cm) peripheral lung cancers,[10,11] and there is still the problem of incomplete hilar lymph node dissection in patients who undergo segmentectomy. In that context, thoracic surgeons have been seeking a more accurate noninvasive method for preoperative nodal staging.

It is a well-known fact that bilateral diffuse FDG (pseudo-) activity in multiple thoracic lymph nodes in patients such as those with chronic inflammation due to pneumonitis or lymphangitis has been misinterpreted as cancer progression. This could obviously have a major impact on the patient's further treatment strategy. The aim of the present study was to use surgical and histological results from patients presenting with localized and clinically resectable advanced lung cancer to assess the efficacy of an I/C-SUV ratio calculated as tumor ipsilateral/contralateral hilar lymph node SUV as a simple noninvasive technique for improving nodal staging.

METHODS

Patients

All experimental protocols were approved by the institutional review board at Akita University Hospital (approval number: 2679), and all samples were collected under the IRB-approved protocol, which allows collection of tissue and medical records with consent or waiver of consent when no personalized health information is required, as was the case in this study. PET/CT findings and clinical/pathological records for patients treated between January 2010 and December 2020 at our University Hospital were retrospectively reviewed. The PET/CT was done for staging lung lesions that were suggestive of lung cancers without distant metastases in earlier clinical or radiological examinations. In total, 182 patients who had undergone major pulmonary resections for pStage IB-III resectable lung cancer were enrolled in the study. The patients with pm3, contralateral double lung cancer, other thoracic cancer, or severe diabetes mellitus who could not be decreased blood sugar level <150 mg/dl just before PET/CT were excluded. All lymph nodes in the mediastinum/hilum of these patients were measured. The patients' characteristics are listed in Table 1. A diagram of the process by which cases were selected for study is shown in Figure 1.

PET/CT measurements of lymph node SUV

All patients underwent PET/CT examination as a routine procedure within 3 months before surgery. PET/CT imaging was performed 60 min after intravenous injection of 120–220 MBq of FDG (Nihon Medi-Physics). All FDG PET/CT images were obtained using a Discovery ST16 PET/CT scanner (GE Healthcare). A diagnostic CT scan for fusion was obtained using a standard protocol without intravenous contrast (120 kV; Auto mA range, 30–250 mA, noise index 25; thickness
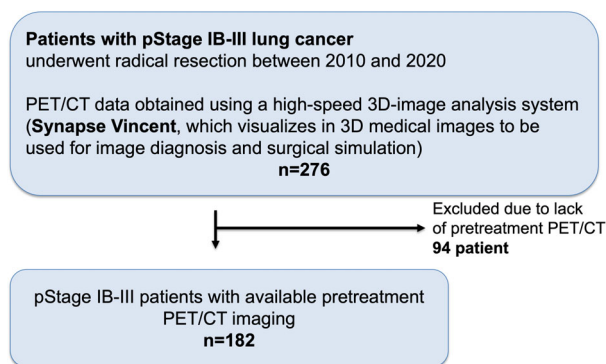

FIGURE 1 Flow chart illustrating subject enrollment protocol

3.75 mm; pitch 1.75; beam collimation 20 mm). Coregistered images were displayed using a high-speed 3D-image analysis system (SYNAPSE VINCENT, Fujifilm Corporation).

FDG positivity in each primary lung tumor was retrospectively evaluated. The SUV_{max} was determined by drawing a region of interest (ROI) around the tumor and within the affected lymph node and using the maximum SUV recorded within each ROI. The SUV was calculated as the activity per millimeter within a ROI divided by the dose injected in MBq/g bodyweight.[12]

New I/C-SUV ratio

To determine the new lymph node SUV ratio, a contralateral hilar lymph node (on the side of the chest opposite that of the primary tumor) was also measured using the SYNAPSE VINCENT software (Figure 2). The I/C SUV ratio was then calculated as ipsilateral hilar node SUV/contralateral hilar node SUV.

All PET/CT images and the SUV_{max} were evaluated by investigators who were blinded to the clinical information. Determining precise correspondence between lymph nodes on imaging and at surgery is a difficult problem when several lymph nodes are sampled within the same station. Therefore, all lymph nodes on PET/CT were measured in each node station, and the uptake node with the highest SUV was selected for the present study. The highest SUV_{max}s in both ipsilateral and contralateral lymph node stations were used for ratio calculation.

Conventional criteria and classification of lymph node metastasis using PET/CT

For evaluations using CT and PET/CT, tumor size, lymph nodes and staging were reclassified based on their location (i.e., mediastinal or hilar) and the 8th edition of the Union Internationale Contre le Cancer (UICC)-TNM staging system.[13] The conventional criterion used for determining lymph node metastasis on PET/CT is a SUV_{max} of 2.5 or

TABLE 1 Patient characteristics

No. of patients		182	(N+ patients; 50.55%)		
Age	(median)	69	Tumor location & surgery		
	range	33–85		RUL	68
Sex	Male	128		RML	4
	Female	54		RLL	26
				LUL	40
Nodal status				LLL	28
cN status	N0	119		RMLL	4
	N1	31		RUML	9
	N2	31		PN	3
pN status	N0	90			
	N1	37			
	N2	55	Pathological stage		
				IB	90
Tumor size	(mm) Mean	34.7 ± 13.6		IIA	0
	min-max	10–85		IIB	32
Type	adeno	129		IIIA	40
	squamous	47		IIIB	20
	others	6		IV	0
			pm status	pm0	175
Measured lymph node		910		pm1	5
including hilar node		364		pm2	2
				pm3	0

Abbreviations: adeno, adenocarcinoma; squamous, squamous cell carcinoma; LLL, left lower lobe; LUL, left upper lobe; PN, pneumonectomy; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.
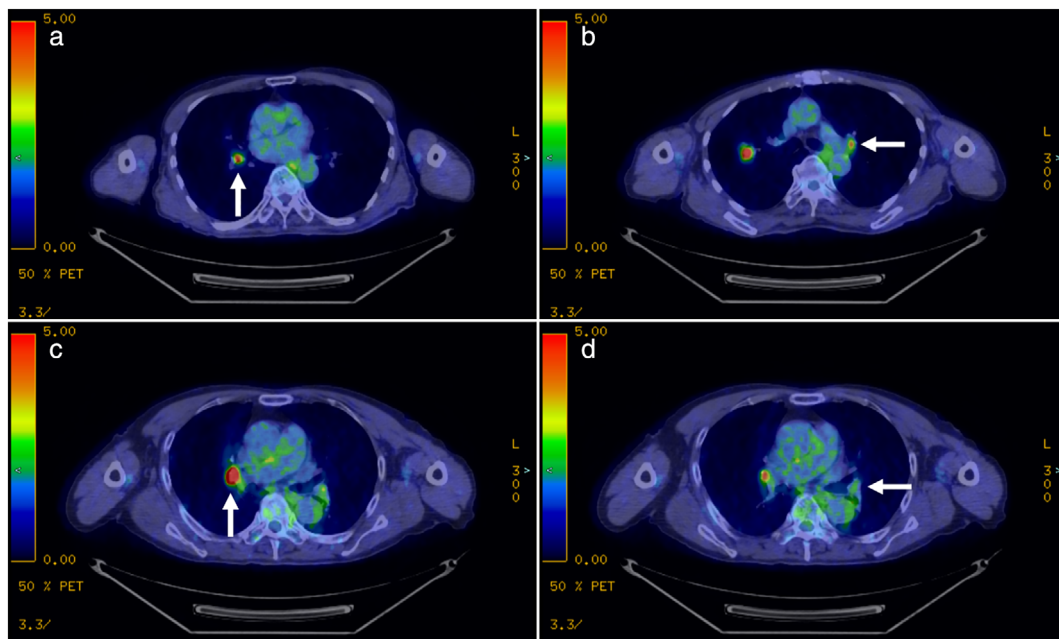

FIGURE 2 Measurement of ipsilateral/contralateral hilar node (I/C)-SUV on PET/CT images. I/C-SUV$_{max}$s from two patients with resectable cancers were measured using caliper software with PET/CT images on a computer screen. In these examples, the SUVs of hilar lymph nodes were measured in a N0 patient (a, b) and a N1 patient (c, d). In the N0 (30 mm adenocarcinoma, pStage IB) case, the ipsilateral hilar node SUV$_{max}$ = 4.31 (a), contralateral hilar node SUV$_{max}$ = 3.69 (b), and I/C-SUV$_{max}$ = 1.17. In the N1 (32 mm squamous cell carcinoma, #12u N+, pStage IIB) case, the ipsilateral hilar node SUV$_{max}$ = 53.0 (c), contralateral hilar node SUV$_{max}$ = 2.67 (d), and I/C-SUV$_{max}$ = 19.85. White arrows show the FDG uptake by the hilar lymph node

larger on axial images.[6–8] Expert radiologists evaluated lymph node metastasis using preoperative PET/CT imaging based on the conventional criterion.

Surgery

In general, lung cancer is treated with segmentectomy, lobectomy or pneumonectomy plus systematic nodal dissection. Even in cases of extensive nodal involvement, complete resection is attempted. Complete resection is defined by presence of both macroscopic and microscopic tumor-free margins.

Pathological evaluation

Two independent pathologists evaluated samples of dissected tissue. All dissected tumors and lymph nodes were sectioned and examined conventionally using hematoxylin–eosin staining and/or immunohistochemistry.

Statistical analysis

Group data are expressed as means ± standard deviation. Differences between the measured SUV_{max} and I/C ratio for metastatic and non-metastatic lymph nodes were evaluated using the Wilcoxon test. Receiver operating characteristic (ROC) curves were used to determine the cutoff values that yielded the highest combined sensitivity and specificity with respect to distinguishing metastatic lymph nodes. The areas under the ROC curves (AUC) were compared using the method described by Hanley and McNeil.[14] The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and AUC were all calculated using standard formulas with a 2 × 2 table of the collected data. 95% CI were calculated using the Clopper-Pearson method. For all tests, values of $p < 0.05$ were considered statistically significant. JMP IN 15.2.0 software (SAS Institute) was used for all statistical evaluations and for drawing the ROC curves.

RESULTS

PET/CT was used to evaluate 364 hilar lymph nodes out of a total of 910 measured nodes (1–4 hilar and mediastinal nodes per patient). The ipsilateral hilar node SUV_{max} and the I/C-SUV ratio were always significantly larger in metastatic lymph nodes than non-metastatic nodes ($p < 0.0001$, Figure 3). By contrast, no significant difference was detected between contralateral hilar node SUV_{max}s ($p = 0.9133$).

To determine the cutoff values that yielded the highest combined sensitivity and specificity with respect to distinguishing metastatic from nonmetastatic lymph nodes, ROC curves were used to analyze the measured parameters (Figure 4). From these analyses, we determined the cutoff value for lymph node metastasis to be 3.0 for the hilar lymph node SUV (LN-SUV) and 1.32 for the I/C-SUV ratio. The thresholds obtained from the ROC curves as well as the sensitivity, specificity, PPV, NPV and accuracy are summarized in Table 2.

Table 3 shows the sensitivity, specificity, PPV, NPV, and accuracy for diagnosis when the I/C-SUV ratio is ≥1.32 or 1.34 in patients with a hilar lymph node and/or primary lung tumor SUV_{max} ≥2.5. When an I/C-SUV ratio of ≥1.32 with a tumor SUV ≥2.5 was used as prerequisite for diagnosis of N1 metastasis, the sensitivity, specificity, PPV, NPV, accuracy and AUC were 46.75% (36 of 77), 87.5% (77 of 88), 76.59% (36 of 47), 65.25% (77 of 118), 68.48% (113 of 165) and 0.6944, respectively. When an I/C-SUV ratio ≥1.34 with a LN-SUV ≥2.5 was used for diagnosis of N1
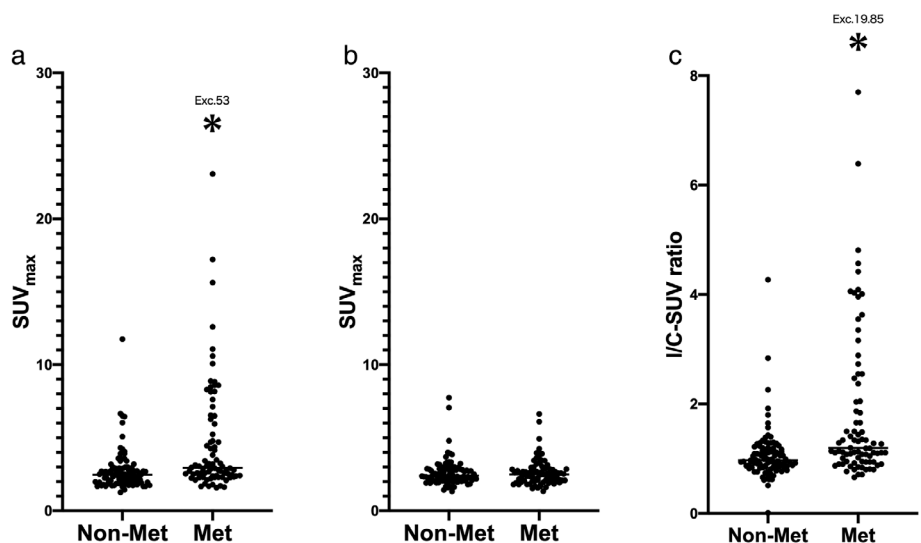

FIGURE 3 Difference between the maximum standardized uptake values (SUV_{max}s) in ipsilateral and contralateral hilar nodes and the I/C-SUV ratio. The ipsilateral hilar node SUV_{max} (a) and I/C-SUV ratio (c) were always significantly larger in metastatic lymph nodes than non-metastatic nodes ($p < 0.0001$). The contralateral hilar node SUV_{max}s (b) did not significantly differ between nodes ($p = 0.9133$). * significant different; Met, metastasis

metastasis, the sensitivity, specificity, PPV, NPV, accuracy and AUC were 60.34% (35 of 58), 82.0% (41 of 50), 79.55% (35 of 44), 64.06% (41 of 64), 70.37% (76 of 108) and 0.6998, respectively. When an I/C-SUV ratio ≥1.34 with a LN/tumor-SUV ≥2.5 was used for diagnosis of N1

metastasis, the sensitivity, specificity, PPV, NPV, accuracy and AUC were 59.65% (34 of 57), 78.05% (32 of 41), 79.07% (34 of 43), 58.18% (32 of 55), 67.35% (66 of 98) and 0.6692, respectively. When an I/C-SUV ratio ≥1.34 with LN-SUV ≥2.5 was used for diagnosis of N1/N2 metastasis, the
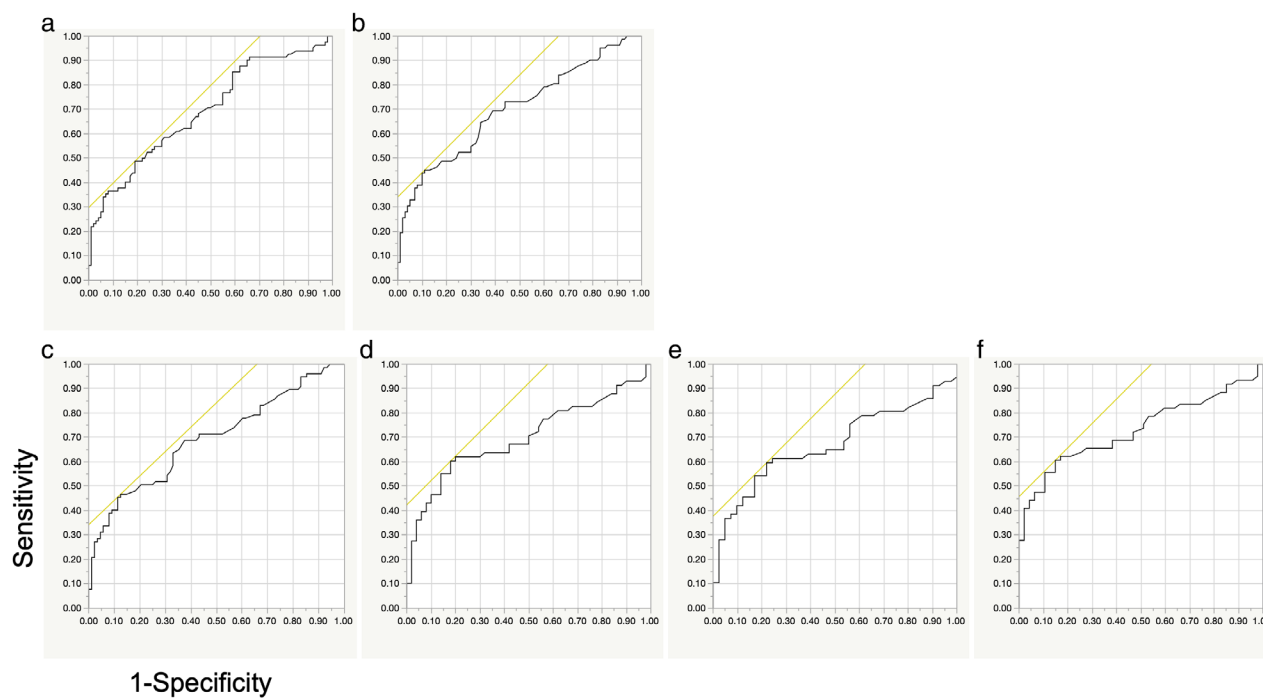

FIGURE 4 Receiver operating characteristic (ROC) curves for detection of lymph node metastasis using PET/CT. Panels (a) and (b) depict the ROC curves for lymph node (LN) SUV_{max} (≥3.0, the best cutoff value) and an I/C-SUV ratio ≥1.32 for all N1 lymph nodes. Panels (c–f) depict the ROC curves for an I/C-SUV ratio ≥1.32 (with tumor SUV ≥2.5) for predicting N1 (C), I/C-SUV ratio ≥1.34 (with LN SUV ≥2.5) for predicting N1 (f), I/C-SUV ratio ≥1.34 (with tumor/LN SUV ≥2.5) for predicting N1 (e), and I/C-SUV ratio ≥1.34 (with LN SUV ≥2.5) for predicting N1/N2 (f). The thresholds obtained from the ROC curves for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy are summarized in Tables 2 and 3

TABLE 2 Diagnosis of hilar lymph node metastasis based on new I/C SUV ratio calculated as ipsilateral hilar node SUV/contralateral hilar node SUV or conventional criteria using simple SUV_{max}s

	Radiologists	Radiologists	Based on ROC	New criteria
Method	LN-SUV ≥2.0	LN-SUV ≥2.5	**LN-SUV ≥3.0**	**SUV ratio ≥1.32**
Sensitivity, %	91.46	70.73	**48.78**	**45.12**
(95% CI)	83.20–96.50	59.65–80.26	37.58–60.08	34.10–56.51
Specificity, %	29.0	51.0	**81.0**	**89.0**
(95% CI)	20.36–38.93	40.80–61.14	71.93–88.16	81.17–94.38
PPV, %	51.37	54.2	**67.79**	**77.08**
(95% CI)	42.97–59.72	44.30–63.88	54.36–79.38	62.69–87.97
NPV, %	80.56	68.0	**65.85**	**66.42**
(95% CI)	63.98–91.81	56.22–78.31	56.76–74.16	57.75–74.34
Accuracy, %	57.14	59.89	**66.48**	**69.23**
(95% CI)	49.61–64.44	52.38–67.07	59.12–73.30	61.98–75.85
AUC	0.6023	0.6087	**0.6926**	**0.6998**
(95% CI)	0.5472–0.6549	0.5370–0.6759	0.6102–0.7642	0.6173–0.7710

Abbreviations: CI, confidence interval; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value.

TABLE 3 Diagnosis of thoracic lymph node metastasis based on I/C SUV ratios and the SUV prerequisite of lymph node and/or primary tumor

Predicting N status	N1	N1	N1	N1/N2
Prerequisite[a]	Tumor-SUV ≥2.5	LN-SUV ≥2.5	LN/tumor-SUV ≥2.5	**LN-SUV ≥2.5**
SUV ratio	≥1.32	≥1.34	≥1.34	**≥1.34**
Sensitivity, %	46.75	60.34	59.65	**60.66**
(95% CI)	35.29–58.48	46.64–72.95	45.82–72.44	47.31–72.93
Specificity, %	87.5	82.0	78.05	**85.11**
(95% CI)	78.73–93.59	68.56–91.42	62.39–89.44	71.69–93.80
PPV, %	76.59	79.55	79.07	**84.09**
(95% CI)	61.97–87.70	64.70–90.20	63.96–89.96	69.93–93.36
NPV, %	65.25	64.06	58.18	**62.5**
(95% CI)	55.94–73.78	51.10–75.68	44.11–71.35	49.51–74.30
Accuracy, %	68.48	70.37	67.35	**71.29**
(95% CI)	60.81–75.48	60.82–78.77	57.13–76.48	61.80–79.59
AUC	0.6944	0.6998	0.6692	**0.7309**
(95% CI)	0.6076–0.7694	0.5914–0.7897	0.5547–0.7667	0.6262–0.8149

Abbreviations: CI, confidence interval; LN, lymph node; NPV, negative predictive value; PPV, positive predictive value.
[a]Each I/C SUV ratio was subset analyzed on the prerequisite that a hilar lymph node and/or primary lung tumor SUV_{max} ≥2.5 was used first.

sensitivity, specificity, PPV, NPV, accuracy and AUC were 60.66% (37 of 61), 85.11% (40 of 47), 84.09% (37 of 44), 62.5% (40 of 64), 71.29% (77 of 108) and 0.7309, respectively.

DISCUSSION

Our ROC curve analyses indicated that an I/C-SUV ratio ≥1.34 on PET/CT best distinguishes nodal status in lung cancer when the hilar LN-SUV is ≥2.5. Clinicians often observe FDG uptake by hilar lymph nodes contralateral to the primary tumor, despite the lack of enlargement of the ipsilateral/contralateral lymph nodes. Although radiologists clearly possess knowledge indicating these patients are not clinical N3, using an I/C-SUV ratio to consider collateral hilar LN FDG uptake, we achieved greater specificity and accuracy than was achieved by experienced radiologists using the conventional criterion SUV_{max} ≥2.5.

When comparing the abilities of CT and PET/CT to detect metastatic lymph nodes, the sensitivity, specificity, and accuracy of PET/CT were 71%–89%, 89%–96%, and 81%–93%, respectively.[15–17] However, nodal staging requires accurate and reliable interpretation of the information provided by PET/CT. A systematic review reported that the sensitivity (17%–100%) and specificity (33%–100%) of FDG-PET varied among studies and centers due differences in the criteria for PET positivity (e.g., LN uptake > mediastinal background, LN SUV_{max} ≥2.5, or "mixed"). Variability also resulted from PET/CT scanners with different performance metrics.[9,18] The sensitivity and specificity of a node SUV_{max} >2.5 were 70.73% and 51.0% in our study. SUV_{max} is a generally useful marker of malignancy, but the best cutoff for staging and prediction varies.[19,20] Moreover, in those

earlier studies other metabolic PET parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), were not sufficiently assessed for staging and prediction.[21] In the present study, we focused on N1 nodal staging. One of the reasons is that anatomic segmentectomy for early (≤2 cm) peripheral lung cancer is an oncologically safe and reasonable alternative to lobectomy, but only when there is adequate intraoperative nodal staging, as surgeons cannot complete the segmental/subsegmental lymph node dissection for the remaining lung segment.[22,23] The new I/C-SUV ratio demonstrated better specificity and should serve as a simple and noninvasive procedure for predicting accurate nodal staging before planning segmentectomy.

Diffusion-weighted magnetic resonance imaging (DWI) is an MRI technique based on imaging of the molecular mobility of water. The reported sensitivity and specificity of DWI for evaluating nodal status are 0.72 (95% CI: 0.68–0.76) and 0.97 (95% CI: 0.96–0.98), respectively.[24] DWI appears to have several advantages over ^{18}F-FDG PET/CT scanning, including the absence of ionizing radiation, no requirement for large installations, shorter examination time (30 min for DWI versus 90 min for PET/CT). Consistent with our results, however, two meta-analyses showed that both PET/CT and DWI have high specificity and low sensitivity for identifying metastatic lymph nodes.[24,25] The new I/C-SUV ratio from PET/CT improves specificity (similarly to DWI) as compared to conventional SUV_{max} alone and provides supportive information that can be used to determine nodal staging and surgical indications.

In recent decades, the emergence of EGFR-targeted tyrosine kinase inhibitor (TKI) therapy[26–30] and immune checkpoint inhibitors (ICIs)[31–34] have been shown to extend survival and improve the quality of life for lung cancer

patients. The primary lesion SUV_{max} had moderate predictive efficacy with respect to EGFR mutation status. Impotantly, the SUV_{max}, total MTV[31] and TLG can be used as potential predictive markers of response in patients with PD-L1-high lung cancer treated with ICIs. PET/CT could be useful for selection of patients who require TKIs or ICIs. To address the issue of heterogeneity, future analyses should analyze postoperative-recurrent lung cancer patients treated with TKIs or ICIs to explore the SUV_{max} and I/C-SUV ratio of recurrent lymph nodes.

Nodal overstaging with PET/CT can be a problem due to the low specificity. In our earlier report,[20] a lymph node SUV ≥2.5 section area (SA)/node SA ratio of ≥1.0 in tumor ipsilateral lymph node was a more accurate level than was achieved using only SUV_{max}. However, the specificity of SUV ≥2.5 SA/node SA ratio was shown 73.4%. Furthermore, two new PET tracers were introduced to improve diagnosis and nodal staging: 3′-deoxy-3′-18F-fluorothymidine (FLT) is used for cellular proliferation imaging,[35] while 4′-[methyl-11C]-thiothymidine (4DST) is incorporated into DNA.[36] FLT or 4DST-PET/CT is more sensitive for detecting mediastinal lymph node metastasis, but it shows lower specificity. Even if using the devised criteria that merely focused on tumor ipsilateral node or new PET tracers, these still will not be able to avoid the influence by chronic inflammation.

This study has several limitations. First, selection bias has to be considered, since only resectable advanced pStage IB–III lung cancer patients eligible for surgical resection were included in our analysis. This inherently heightens the prevalence of lymph nodal involvement. Second, an important limitation of the new criterion is that the sensitivity could not be improved beyond that achieved using the conventional criterion of SUV_{max} ≥2.5. However, sensitivity does not provide the basis for informed decisions following positive screening test results because those positive test results may contain many false positive outcomes. Conversely, specificity does not provide an accurate indication about a negative screening test result because negative outcomes from a screening test may contain many false negative results. Negative results from highly sensitive tests can rule a diagnosis out (sensitive, negative, out = SnNOut), and positive results from highly specific tests can rule a diagnosis in (specific, positive, in = SpPIn).[37,38] This study analyzed N+ patients (50.55%) with high pretest probability for lymph node metastasis. The new I/C SUV ratio has great specificity (SpPIn property) and supports lymph node metastasis if the SUV ratio is ≥1.34, which means positive. The ROC curve displays the full picture of trade-off between the sensitivity and specificity. A positive result on higher-specificity test is essential for nodal staging in patients with clinically suspected hilar lymph node metastasis. Third, the study did not include patient underwent endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) before surgery. The event of Non-N3 was presumed by only patient follow-up. EBUS-TBNA may be a good backup plan, as mediastinoscopy is difficult to detect hilar lymph nodes.

In summary, an I/C-SUV ratio ≥1.34 achieved good specificity and accuracy and improved nodal staging in resectable advanced lung cancers. In a situation where N1 nodes are not enlarged but FDG uptake is high, hilar lymph node staging must be assessed intraoperatively at the time of resection, with the possible exception of small preinvasive or minimally invasive lung cancers, especially when performing a sublobar resection. Our findings indicate that the new I/C-SUV ratio from PET/CT is a simple and noninvasive procedure that can serve as a guide for appropriate therapeutic strategies in daily clinical practice or for lymph node dissection in lung cancer surgery. I/C ratio has the potential to resolve the misinterpretation as cancer progression by bilateral diffuse FDG (pseudo-) activity due to chronic inflammation in multiple thoracic lymph nodes.

CONFLICT OF INTEREST
The authors declare that they have no competing interests with respect to the research, authorship, and/or publication of this article. The authors have no financial conflict of interest.

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