Use of Maximum Standardized Uptake Value on Fluorodeoxyglucose Positron-emission Tomography in Predicting Lymph Node Involvement in Patients with Primary Non-small Cell Lung Cancer

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Abstract. *Aim: Surgical resection is a standard therapeutic approach for some cases of non-small cell lung cancer (NSCLC). Fluorodeoxyglucose positron-emission tomography (FDG-PET) is now widely used in clinical diagnosis and staging of various types of cancers, including NSCLC. We investigated whether the maximum standardized uptake value (SUV_{max}) of primary tumors is useful in predicting the extent of lymph node involvement. Patients and Methods: We retrospectively evaluated 354 patients with NSCLC who underwent surgery following FDG-PET and computed tomographic (CT) scans in our hospital. Logistic regression analyses were used to assess associations between categories (age, sex, tumor size, SUV_{max}, serum Squamous cell carcinoma-related antigen (SCC), cytokeratin 19 fragment (CYFRA), carcinoembryonic antigen (CEA), Brinkman index and histologic type. Differences in SUV_{max} of primary tumors between positive and negative lymph node involvement were examined by Mann–Whitney U-test. Results: SUV_{max} of primary tumors in patients without lymph node involvement was significantly lower than in those with involvement, in both adenocarcinoma and squamous cell carcinomas (median, 2.2 vs. 4.9 in adenocarcinoma and 5.0 vs. 8.1 in squamous cell carcinoma, $p<0.001$ for both). Among node-positive cases, the lowest primary tumor SUV_{max} was 1.24 in an adenocarcinoma and 2.05 in a squamous cell carcinoma. However, primary tumor SUV_{max} and extent of lymph node metastases showed no significant differences between pN1 and pN2, single and multiple lymph node involvement, or single and multiple station involvement. Conclusion: A low primary tumor SUV_{max} in NSCLC may help identify patients with no lymph node involvement. However, SUV_{max} does not discriminate between minimal and extended lymph node involvement.*

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Lung cancer remains the most common cause of cancer-related deaths worldwide, with an estimated survival of only 15% at five years (1). Treatment of lung cancer is guided by clinical staging. Surgical treatment is the standard therapeutic approach for most resectable non-small cell lung cancers (NSCLC). However, involvement of mediastinal lymph nodes (LN) in patients with lung cancer is the most important prognostic factor in the absence of distant metastases (2, 3). Accurate diagnosis of LN metastasis is critical in deciding on optimal treatment; complete LN excision with microscopic evaluation is thought to be the most accurate method for determining LN metastasis. Both sampling and systematic LN dissection are reportedly associated with increased incidence of complications, such as atrial arrhythmias, prolonged air leaks, and excessive chest tube drainage (4). As new TNM classifications imply that very small lung carcinomas are less aggressive than others (5) and require less aggressive surgical approaches, benefits of mediastinal lymphadenectomy remain controversial.

18F-Fluorodeoxyglucose positron-emission tomography (FDG-PET) is now widely used in clinical diagnosis and staging of various types of cancer, including NSCLC. Integrated FDG-PET scans can diagnose the presence of LN metastasis more accurately than computed tomographic (CT) scans alone. A multi-center randomized trial proved the utility of preoperative PET scan in patients with suspected lung cancer (6).

Although the negative predictive value of FDG-PET is as high as 86%, false negatives for LN involvement are 14%, which is too high to be ignored (7). The maximum standardized uptake value (SUV_{max}) reportedly correlates with cell proliferative activity and malignancy (8), and LN involvement (9). Thus, we hypothesized that primary tumor SUV_{max} might predict the extent of LN involvement. The purpose of this study was to investigate the relationship between FDG uptake in the primary tumor and LN involvement.

Patients and Methods

Patients. Between May 1999 and December 2008, 547 patients with NSCLC underwent resection in our hospital. Of the original 547 patients, 193 were ultimately removed from the study for having no preoperative FDG-PET, FDG-PET being performed at another hospital, or history of induction therapy. We retrospectively evaluated 354 patients with NSCLC who underwent lung resection following FDG-PET and CT at our hospital (Table I). All variables were collected retrospectively from patients' records. The Institutional Review Board waived the need for written informed consent because of the retrospective nature of this study.

Diagnostic imaging. Total body FDG-PET and CT were used to determine clinical staging, using the TNM classification (seventh edition) (5). Clinical and pathological staging based on the fifth or sixth editions was re-classified according to the seventh edition. Maximum lung nodule diameters were measured on axial CT images. We also preoperatively judged the LN station as metastatic if the short-axis diameter of the lymph node was greater than 10 mm on the axial CT view, as in a previous report (10). Each patient with NSCLC who was a potential candidate for thoracic surgery underwent a dedicated chest CT scan and an FDG-PET. Both investigations were independently assessed by two radiologists.

The CT examinations were performed using an Aquilion CT scanner (Toshiba, Tokyo, Japan). All patients underwent enhanced CT after intravenous administration of contrast material, unless they were allergic to it. Five-millimeter-thick contiguous image sections were obtained.

FDG-PET was performed using a whole-body scanner (ECAT EXACT HR+; Siemens/CTI, Knoxville, TN, USA) with a transaxial field of view of 15.5 cm (spatial resolution 4.5 mm). Prior to FDG-PET, patients fasted for at least 6 h. Whole-body emission images were obtained 60 min following injection of 4.5 MBq/kg 18-FDG using the three-dimensional acquisition method for two minutes per bed emission scan. All patients were asked to remain resting and quiet, and to void just before scanning. These images were reconstructed by ordered-subsets expectation maximization (OSEM) method with attenuation correction. Attenuation correction was performed using a three-minute transmission scan, instead of using SUV_{max}.

All patients underwent complete resection, including wedge resection in 51 patients (14%), segmentectomy in 21 (6%), lobectomy in 264 (75%), bilobectomy in 4 (1%), and pneumonectomy in 14 (4%).

Table I. *Characteristics of patients*.

	Lymph node metastasis		
	–	+	Total
Characteristic	N=273	N=81	N=354
Gender			
Male	153	59	312
Female	120	22	142
Median age (range), years	67 (31-92)	68 (38-85)	
Median tumor size (range), mm	24 (5-100)	34.5 (11-81)	
Histological type			
Adenocarcinoma	163	47	210
Adenosquamous carcinoma	6	4	10
Squamous cell carcinoma	66	28	94
Bronchioloalveolar carcinoma	25		25
Large cell carcinoma	6		6
Other	7	2	9
Operative procedure			
Partial resection	45	6	51
Segmental resection	16	5	21
Lobectomy	207	57	264
Bilobectomy	4	0	4
Pneumonectomy	1	13	14
Pathological stage			
IA	159	0	159
IB	72	0	72
IIA	10	20	30
IIB	25	2	27
IIIA	3	52	55
IIIB	0	5	5
IV	4	2	6

Systematic mediastinal LN dissection was performed with segmentectomy, lobectomy, bilobectomy and pneumonectomy. The LN statuses of 51 patients who underwent wedge resection without mediastinal LN dissection were classified as rN0 after two years without locoregional LN recurrence. If patients without LN dissection developed locoregional LN recurrence within two years after resection, they were classified as rN1 or rN2 according to the LN station involved (Table II). The LN stations were classified according to the original Naruke's LN map of lung cancer (11).

We investigated correlation between SUV_{max} and the extent of LN metastasis with such indicators as N factor (N0, N1, or N2), number of LNs involved (negative, single, or multiple) and number of stations involved (negative, single, or multiple) in resected NSCLC.

Statistical analysis. Logistic regression analyses were used to assess associations between age, sex, tumor diameter, SUV_{max}, Brinkman index (BI), histological type, preoperative serum Squamous cell carcinoma-related antigen (SCC), Cytokeratin 19 fragment (CYFRA), and Carcinoembryonic antigen (CEA). Differences in primary tumor SUV_{max} between those with and and those without LN involvement were analyzed by Mann–Whitney *U*-test. All analyses were performed with STAT FLEX software, version 6 (Artech Co., Ltd. Osaka. Japan). A *p*-value of less than 0.05 was considered statistically significant.

Table II. *N factors based on pathological diagnosis and post-operative recurrence.*

	N	pN	rN
N0	318	273	45
N1	46	46	0
N2	41	35	6

pN, Pathological N; rN, patients without mediastinal LN dissections were classified as rN0, rN1 and rN2 after two years according to location of nodal recurrence, *i.e.* rN0, no LN recurrence; rN1, recurrence to N1 lymph nodes; rN2, recurrence to N2 lymph nodes.

Results

Patients' characteristics and pathological features of nodal involvement are listed in Table I. Histological types were adenocarcinoma in 210 (59.3%), squamous cell carcinoma in 94 (26.6%), bronchioloalveolar carcinoma in 25 (7.1%), large cell carcinoma in 6 (1.7%), adenosquamous carcinoma in 10 (2.8%), and other types in nine (2.5%). Univariate analyses for factors significantly associated with LN metastasis were: sex (p=0.008), tumor diameter (p<0.001), SUV_{max} (p<0.001, Table III). The multivariate analysis identified primary tumor SUV_{max} (p<0.001) as a unique independent risk factor for LN involvement (Table IV). Figure 1 shows the receiver operating characteristic (ROC) curves for LN involvement and the respective factors. The area under the curve (AUC) was calculated from the ROC curves of the diagnostic performance of preoperative factors. The AUC for SUV_{max} was 0.77, which was the highest among the factors investigated.

In the 354 patients, primary tumor SUV_{max} in patients without LN metastases were significantly lower than in those with LN metastases (median, 2.9 *vs.* 6.1, p<0.001; Figure 2A). Among LN-positive cases, the lowest primary tumor SUV_{max} was 1.24 in an adenocarcinoma. Among both adenocarcinomas and squamous cell carcinomas, SUV_{max} of primary tumors in patients without LN metastases was significantly lower than in those with metastases (2.2 *vs.* 4.9 in adenocarcinoma and 5.0 *vs.* 8.1 in squamous cell carcinoma, p<0.001 for both; Figure 2B and C). There was no LN metastasis in patients with squamous cell carcinomas with SUV_{max} less than 2.05. As for primary tumor SUV_{max} and the extent of LN involvement, there were no significant differences between N1 and N2, single and multiple LN, or single- and multiple-station cases (Figure 3).

Discussion

This study shows that SUV_{max} of the primary tumor in cases with LN metastasis is higher than for those with tumors without LN involvement. The SUV_{max} may be predictive for LN metastasis, not only in NSCLC but also in adenocarcinomas and squamous cell carcinomas in other tissues. Cut-off values for prediction of LN involvement are different between adenocarcinoma and squamous cell carcinoma. Although SUV_{max} is significantly associated with LN involvement, it does not seem to correlate with the extent of LN involvement. Ishibashi *et al*. reported that a malignant lung tumor with higher SUV_{max} has a significantly higher probability of intratumoral vessel invasion and LN metastasis, particularly for adenocarcinoma (12). Our results correspond with these data for LN metastasis.

Adenocarcinoma and squamous cell carcinoma are the two major types of NSCLC. Pulmonary squamous cell carcinoma has been shown to have higher SUV_{max} than adenocarcinoma (13); our results are consistent with previous studies. In positive LN specimens, squamous cell carcinoma SUV_{max} is higher than that of adenocarcinoma. To predict LN metastasis, cut-off levels must be set for each pathological tumor type.

Table III. *Univariate analyses for factors associated with lymph node metastasis.*

Characteristic	Odds ratio	95% confidence interval	p-Value*
Gender	2.099	1.217-3.622	0.008
Age	0.999	0.975-1.024	0.959
Maximum diameter	1.039	1.022-1.055	<0.001
SUV_{max}	1.309	1.209-1.418	<0.001
CEA	1.017	0.999-1.035	0.051
SCC	1.094	0.990-1.209	0.077
CYFRA	1.051	0.997-1.109	0.066
BI (≥600)	1.642	0.984-2.739	0.057
Ad/Non-Ad	1.600	0.961-2.665	0.070

CEA: Carcinoembyonic antigen; SCC: squamous cell carcinoma-related antigen and CYFRA: cytokeratin 19 fragment; BI: Brinkman index; Ad: adenocarcinoma. *Logistic regression analysis.

Table IV. *Multivariate analysis for factors associated with lymph node metastasis.*

Characteristics	Odds ratio	95% confidence interval	p-Value*
Gender	1.344	0.641-2.817	0.434
Maximum diameter	1.015	0.995-1.036	0.143
SUV_{max}	1.210	1.105-1.326	<0.001
CEA	1.002	0.980-1.023	0.881
CYFRA	0.982	0.915-1.053	0.607
SCC	1.023	0.926-1.131	0.645
B.I. (≥600)	1.021	0.589-2.448	0.615
Ad/Non-Ad	0.643	0.324-1.277	0.207

CEA: Carcinoembyonic antigen; SCC: squamous cell carcinoma-related antigen and CYFRA: cytokeratin 19 fragment; BI: Brinkman index; Ad: adenocarcinoma. *Multivariate logistic regression analysis.

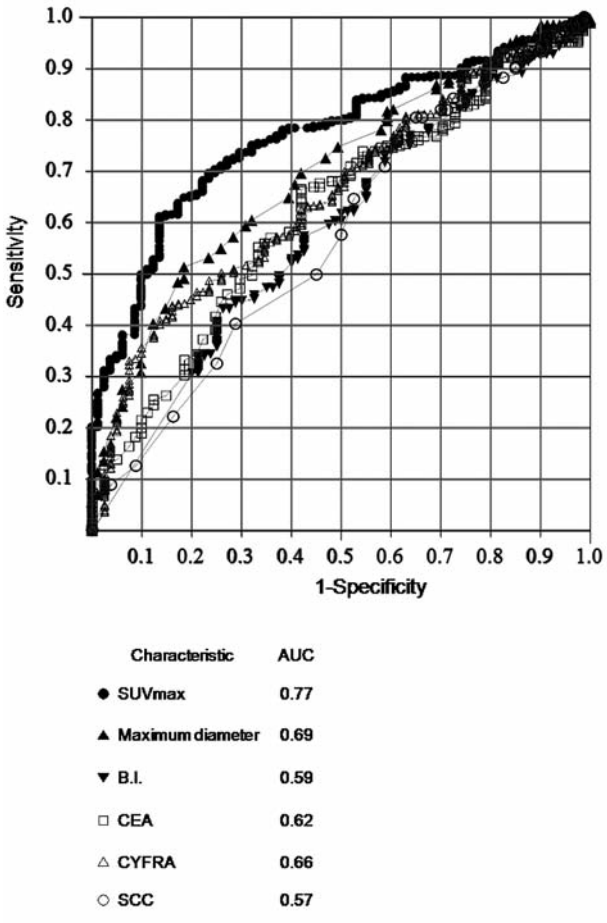

Figure 1. *Receiver operating characteristic (ROC) curves from various clinical factors. The AUC of ROC curve for the maximum standardized uptake value (SUV_{max}) was 0.77. BI, Brinkman index.*

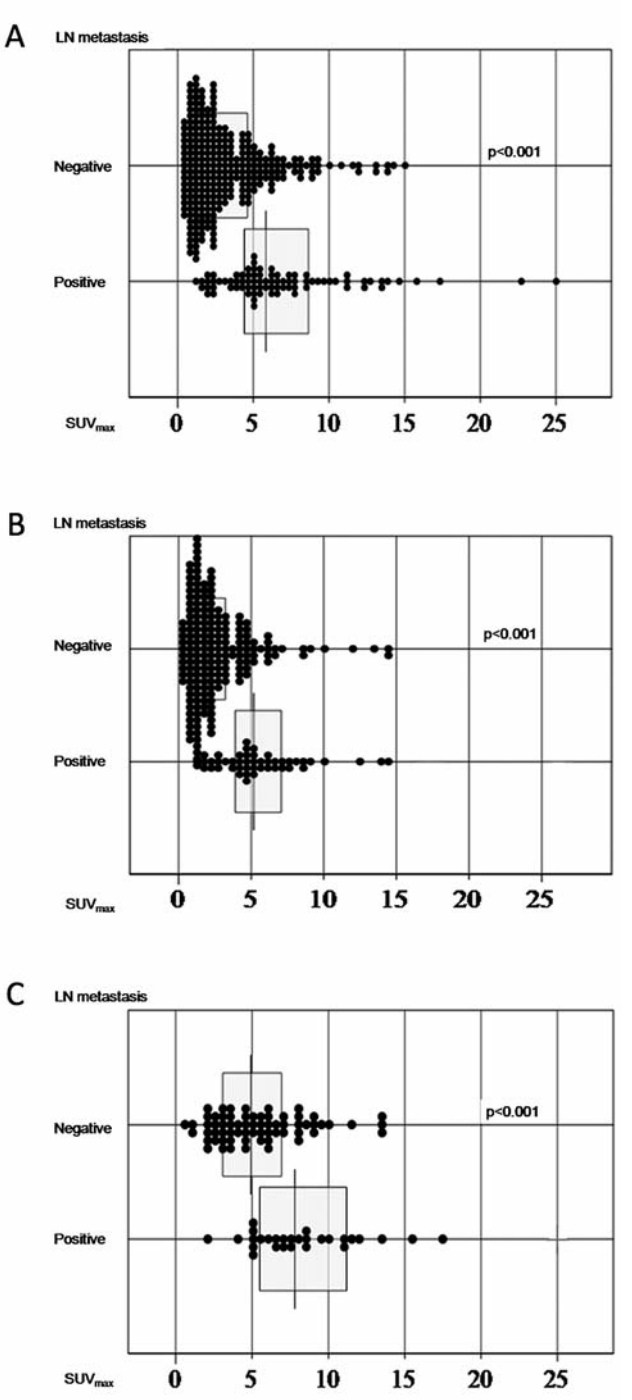

Figure 2. *Lymph node (LN) involvement and the maximum standardized uptake value (SUV_{max}). A: In 354 patients with, primary tumor SUV_{max} in patients without LN metastases was significantly lower than in those with LN metastases. B: Of the 235 patients with adenocarcinoma, the lowest primary tumor SUV_{max} from a patient with LN metastasis was 1.24. Primary adenocarcinoma SUV_{max} in patients without LN metastases was significantly lower than in those with metastases. C: Of the 94 patients with squamous cell carcinoma, primary tumor SUV_{max} in those without LN metastases was significantly lower than in those with LN metastases.*

Among our samples positive for LN metastasis, the lowest primary tumor SUV_{max} was 1.24, in an adenocarcinoma. In squamous cell carcinoma with LN involvement, the lowest primary tumor SUV_{max} was 2.05. Cut-off values could be set for different histological subtypes, although data from different institutions would need to be validated. A recent study by Pastorino *et al*. found that the 5-year survival of patients with lung cancer was 100% for those with nodules with SUV <2.5, suggesting the clinical value of SUV in predicting long-term survival (14). In Ishida *et al*.'s study, 17% of tumors of size of 1-2 cm were also associated with occult LN involvement, whereas no tumors smaller than 1 cm had LN metastases (15). Divisi *et al*. recently found that PET-CT improves identification and characterization of potentially malignant pulmonary nodules with diameter of less than 1 cm using a SUV_{max} cut-off of 2.5 (16); however, PET has poor spatial resolution compared with other imaging modalities such as CT and magnetic resonance imaging

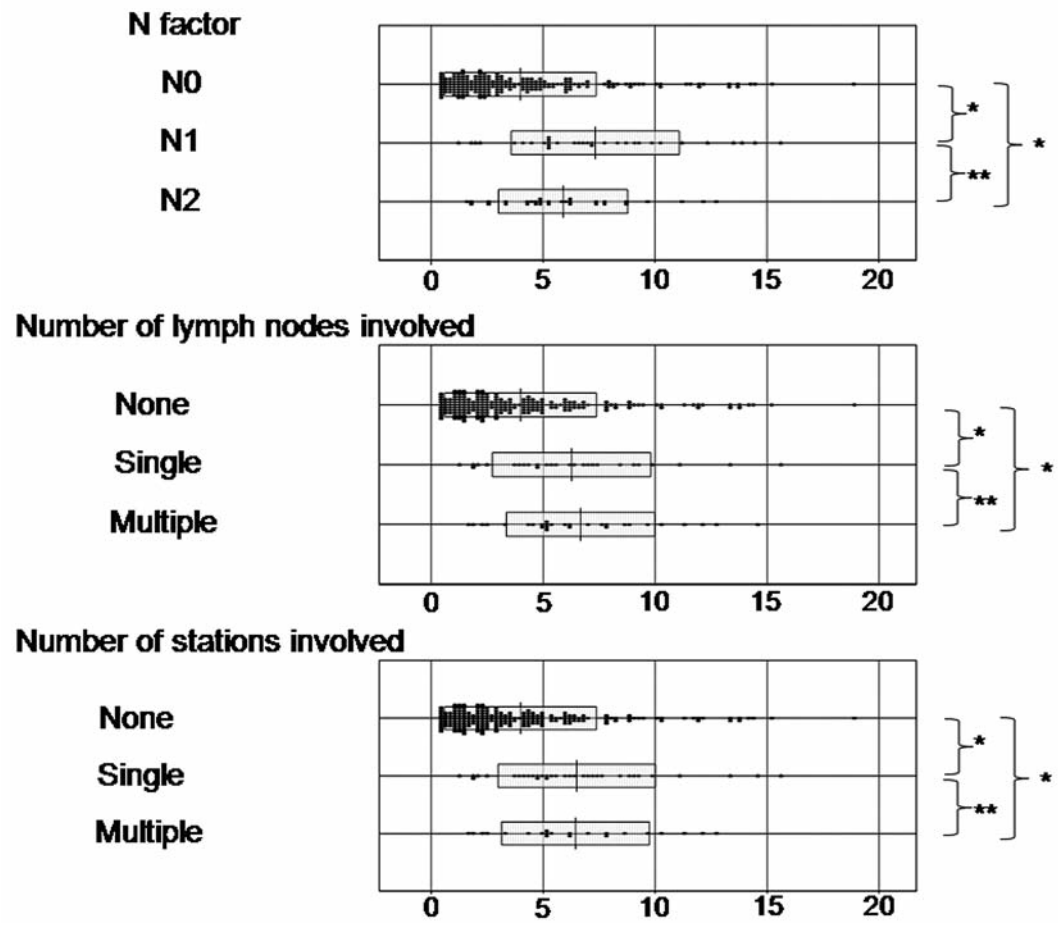

Figure 3. *Primary tumor the maximum standardized uptake value (SUV_{max}) and extent of lymph node (LN) involvement. There were no significant differences between N1 and N2, single and multiple involved LN, or single- and multiple-station involvement. *p<0.01; **not significant.*

(MRI). Because of variations in SUV quantification among Institutions, the optimal cut-off value for SUV_{max} is difficult to set; this might be addressed using a phantom study (17). In our Institute, we would set SUV_{max} of primary NSCLC as less than 1 as a criterion to omit LN dissection. It would be appropriate to set a higher criterion as SUV_{max} of less then 2 for squamous cell carcinoma when more data are available.

The number of involved LNs is an important prognostic factor for NSCLC (18-20). Our study found no statistical differences in primary tumor SUV_{max} between cases of N1 and N2, single and multiple LN metastases, or single and multiple stations of LN involvement; SUV_{max} would not be useful to predict the extent of LN metastasis or to decide the extent of LN dissection.

We believe the primary tumor SUV_{max} is useful in predicting LN involvement in NSCLC, but that SUV_{max} would not be useful in predicting its extent. Our results suggest that LN dissection could be omitted if the primary tumor SUV_{max} is less than 1.

There were some limitations to our study. Firstly, patients with the least chance of LN involvement and deteriorating health condition underwent limited resection without mediastinal LN dissection. We used 2-year locoregional recurrence-free N0 status as an equivalent to pathological N0, although undissected LNs might develop later occurrences. Secondly, this was a retrospective investigation with a limited number of patients in a single Institute. A prospective multi-Institutional study with a large patient cohort would be required to confirm our observations.

Conclusion

We have shown that low primary SUV_{max} in NSCLC may be useful in preoperatively identifying patients who do not need LN dissection. However SUV_{max} does not discriminate between minimal and extensive LN involvement. Cut-off values for omitting LN dissection could be set for different histological subtypes of NSCLC.

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