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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Standardized Uptake Values in the Primary Lesions of Non-Small-Cell Lung Cancer in FDG-PET/CT Can Predict Regional Lymph Node Metastases

Haruhiko Nakamura, MD, PhD[1], Hisashi Saji, MD, PhD[1], Hideki Marushima, MD, PhD[1], Hiroyuki Kimura, MD[1], Rie Tagaya, MD, PhD[1], Noriaki Kurimoto, MD, PhD[1], Masahiro Hoshikawa, MD, PhD[2], and Masayuki Takagi, MD, PhD[2]

[1]Department of Chest Surgery, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan; [2]Department of Pathology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan

ABSTRACT

Purpose. Maximum standardized uptake values (SUV_{max}) at the primary lesions of non-small-cell lung cancer in ^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT), and the microscopic local extension of tumors were examined to develop reliable criteria to determine candidates for sublobar resection.

Methods. We retrospectively analyzed 209 patients who underwent lobectomy, bilobectomy, or pneumonectomy with systematic lymph node dissection. Preoperative SUV_{max} at the primary lesion, microscopic lymphatic, venous, and pleural invasion in addition to lymph node metastases in the resected specimens were examined. Receiver operating characteristic analyses were used to predict an optimal cutoff for lymph node metastases.

Results. With receiver operating characteristic analysis, the areas under the curve for SUV_{max} and tumor size were 0.693 and 0.545, respectively, suggesting SUV_{max} superiority for prediction of lymph node metastases with a cutoff of 2.9. When a tumor was $\leq$2.0 cm ($n = 41$, 19.6 %), the percentages of microscopic lymphatic invasion, venous invasion, pleural invasion, and lymph node metastases were 12.2, 7.3, 4.9, and 17.1 %, respectively. When SUV_{max} was $<$3.0 ($n = 91$, 43.5 %), these percentages were 15.4, 3.3, 7.7, and 8.8 %, showing that SUV_{max} could efficiently exclude nodal metastases in more cases than tumor size. The postoperative 5-year survival rate was 86.6 % in patients with $SUV_{max} < 3.0$ and 58.1 % in patients with $SUV_{max} \geq 3.0$ ($p < 0.001$).

Conclusions. ^{18}F-FDG uptake value was more useful than tumor size for selecting patients with non-small-cell lung cancer suitable for intentional sublobar resection.

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H. Nakamura, MD, PhD
e-mail: h-nakamura@marianna-u.ac.jp

According to a North American randomized, controlled study, the results of sublobar resection were inferior to those of standard lobectomy in clinically node-negative non-small-cell lung cancers (NSCLC) that were $\leq$3 cm in the largest dimension.[1] Nonetheless, limited resection remains an attractive, organ-sparing option that can preserve the lung function and reduce postsurgical morbidity and mortality.[2] The major problem is an increased rate of intrathoracic local recurrences with limited resection than with lobectomy accompanied by the systematic dissection of lymph nodes. These recurrences probably result from the microscopic spread of cancer cells near resected tumor margins and/or micrometastases in the regional lymph nodes left unresected during these procedures. However, sublobar resection could be performed with curative intent if we could preoperatively identify patients who still had cancer cells at the primary site without major infiltration into the adjacent lung parenchyma and who were without regional lymph node metastases.

The longest dimension of a lung cancer is a representative factor commonly used to select appropriate patients for limited resection. However, as previously pointed out, even small tumors ($\leq$2 cm) may be accompanied by lymph node metastases in 15–20 % of cases.[3] In a recent population-based retrospective study, lobectomy showed a significantly favorable 5-year overall and cancer-specific survival for tumors $\leq$2 cm, compared to segmentectomy.[4] Accordingly, alternative factors reflecting the biologic

malignant potential of lung cancer cells other than tumor size should be evaluated to refine the indications for limited surgery in NSCLC.

Pretreatment ^{18}F-fluorodeoxyglucose positron emission tomography integrated with computed tomography (FDG-PET/CT) is useful in localizing various malignant tumors, including primary lung cancers, and the maximum standardized uptake value (SUV_{max}) provides a semiquantitative index of FDG uptake at specific local sites in the body. Cancer cells typically demand energy from the glucose metabolism to meet the demands of their accelerated proliferation, and the accumulation of FDG in malignant tumors reflects intake mechanisms in the cell membrane controlled by the up-regulation of hexokinase enzyme activity.[5,6] The increased FDG uptake in cancer cells is closely associated with their growth and aggressiveness. Numerous clinical studies on lung cancer have demonstrated a significant association between SUV_{max} and tumor growth, disease-stage progression, prognosis, and recurrence rates.[7–12] Therefore, we believed that SUV_{max} may have a potential use as a preoperative indicator of overall malignant potential of NSCLC. If SUV_{max} is low, the tumor may not be highly aggressive and could be completely resected with a minimally invasive limited resection, such as a wedge resection or a segmentectomy without radical lymph node dissection.[13,14] Thus, we retrospectively analyzed the relationship between SUV_{max} and several representative pathologic factors, particularly microscopic lymph node metastases, in comparison with the tumor size.

PATIENTS AND METHODS

Patients

This retrospective study was approved by the institutional review board of St. Marianna University School of Medicine. A total of 209 patients from January 2007 to December 2011 who underwent lobectomy, bilobectomy, or pneumonectomy with systematic lymph node dissection (ND2a) for NSCLC after preoperative FDG-PET/CT at our hospital were included in this study (Table 1). Cases with preoperative induction therapy or multiple lung cancers were excluded. A final diagnosis of NSCLC was obtained from resected lung specimens in all cases. Patients included 117 men and 92 women (age range 27–84 years; mean age 67.1 years). Histologic types were adenocarcinoma in 151 patients, squamous cell carcinoma in 33, large cell carcinoma in 8, and other in 17. Clinical stages were IA in 92, IB in 83, IIA in 8, IIB in 16, and IIIA in 10. A total of 1296 lymph nodes (mean ± SD, 6.2 ± 3.1 per patient) were resected for histologic examination. The mean postoperative follow-up period was 28 ± 17 months.

TABLE 1 Profiles of 209 non-small-cell lung cancer patients who underwent surgery after FDG-PET/CT

Characteristic	Variable	Value
Age (years), mean (range)		67.1 (27–84)
Gender	Female	92 (44.0 %)
	Male	117 (56.0 %)
Histologic type	Adenocarcinoma	151 (72.2 %)
	Squamous cell carcinoma	33 (15.8 %)
	Large cell carcinoma	8 (3.8 %)
	Other	17 (8.1 %)
Clinical stage	IA	92 (44.0 %)
	IB	83 (39.7 %)
	IIA	8 (3.8 %)
	IIB	16 (7.7 %)
	IIIA	10 (4.8 %)
	IIIB	0
	IV	0
Surgery	Lobectomy	193 (92.3 %)
	Bilobectomy	7 (3.3 %)
	Pneumonectomy	9 (4.3 %)

FDG-PET/CT fluorodeoxyglucose positron emission tomography integrated with computed tomography

Imaging Using FDG-PET/CT

FDG-PET/CT was performed as described in our previous report using three types of integrated PET/CT scanners (Eminence-G SOPHIA 3000GCT/M, Shimazu, Tokyo, Japan; Biograph DUO LSO, Siemens, Berlin, Germany; or ECAT ACCEL, Siemens, Berlin, Germany).[15] After fasting for 5 h, patients were given 150–300 MBq FDG intravenously according to the body weight, with PET testing 1 h later. Patients with blood glucose concentrations exceeding 200 mg/dL at the time of the examination were excluded. PET scanning time was 3.5 min per image slice; the slices were obtained from the vertex of the skull to the midthigh. SUV_{max} for each suspicious lesion was automatically calculated after delineation of the area of interest on the attenuation-corrected FDG-PET/CT images. FDG-PET/CT diagnosis, including evaluation of nodal metastases (PET-determined N-factor), was completed by experienced radiologists. A lymph node was considered positive if its localized FDG uptake differed from that of the surrounding normal tissue.

Evaluation of Clinical Stage

The preoperative clinical stages of patients were determined according to the most recent international staging criteria for lung cancer that were published by the International association for the study of lung cancer (IASLC)

in 2009.[16] The longest dimension of the primary tumor, measured as the tumor size on a preoperative chest CT in a lung field window setting, was used to determine the T-factor. The final clinical N-factor (c-N) was determined by measuring the shortest dimension of the hilar and mediastinal lymph nodes on a chest CT in a mediastinal window setting, regardless of PET results; nodes >10 mm were considered positive. The M-factor was determined by the results of the whole-body PET/CT plus brain magnetic resonance image or brain CT.

Pathologic Examination for Local Tumor Invasion

In addition to the pathologic examination of the dissected lymph nodes, microscopic tumor invasion was evaluated according to the IASLC criteria.[15] Those criteria were assessed as follows: absence of lymphatic invasion (Ly0); presence of lymphatic invasion (Ly1); absence of microscopic venous invasion (V0); presence of microscopic venous invasion (V1); or presence of macroscopic venous invasion (V2). Pleural invasion status was considered tumor confined within subpleural lung parenchyma or invading superficially into pleural connective tissue beneath the elastic layer (PL0); tumor invading beyond the elastic layer (PL1); tumor invading to the pleural surface (PL2); or tumor invading into any component of the parietal pleura (PL3) in the resected lung specimen.

Statistical Analysis

Values between two groups were compared by the nonparametric Mann–Whitney *U* test. Values between multiple groups were compared by the Kruskal–Wallis test. Significance in a 2 × 2 contingency table was tested by the χ^2 test. Diagnostic efficiency was analyzed by drawing the receiver operating characteristic curves, and the area under the curve was calculated using Wilcoxon estimates. Survival rate after surgery was calculated by the Kaplan–Meier method, and survival differences between patient groups were tested by the Logrank test. A p value of <0.05 was considered significant for all statistical tests.

RESULTS

Numbers of patients studied with each PET/CT scanner included 63 with Sophia, 37 with Biograph, and 109 with ECAT. The individual PET/CT scanners showed no statistically significant difference among one another in measured SUV_{max} ($p = 0.5914$) in addition to patient subgroups defined by gender, tumor size, histologic type, or disease stage, suggesting that the differences among PET/CT scanners should have had negligible effects on SUV_{max} measurements in the various clinicopathologic categories.

TABLE 2 Relationship among postoperative pathologic N factor (pN), preoperative PET/CT-determined N factor, and final clinical N factor (cN)

Characteristic	PET/CT N factor		cN factor by size of lymph nodes	
	N0	N1–3	N0	N1–3
pN0	145	19	159	5
pN1–3	28	17	39	6
Sensitivity	37.8 %		13.3 %	
Specificity	88.4 %		97.0 %	
PPV	47.2 %		54.5 %	
NPV	83.8 %		80.3 %	

PET/CT positron emission tomography/computed tomography, *PPV* positive predictive value, *NPV* negative predictive value

The postoperative pathologic stages of patients were IA in 103, IB in 40, IIA in 14, IIB in 18, IIIA in 33, and IV in 1. When pathologic lymph node metastases were used as the gold standard, the lymph node metastases evaluated by FDG uptake at hilar and mediastinal lymph nodes demonstrated that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 37.8, 88.4, 47.2, and 83.8 %, respectively (Table 2). For the c-N factor determined by the size of regional lymph nodes, these values were 13.3, 97.0, 54.3, and 80.3 %; suggesting that both FDG uptake in lymph nodes and the size of lymph nodes were unsatisfactory to correctly identify the pathologic lymph node metastases.

For pathologic lymph node metastases, receiver operating characteristic analysis indicated that areas under the curve determined by SUV_{max} for primary lesions and tumor sizes were 0.693 [95 % confidence interval (CI) 0.611–0.775] and 0.545 (95 % CI 0.449–0.641), respectively (Fig. 1).The optimum cutoff point for SUV_{max} was 2.9, and the cutoff for tumor size was 3.5 cm. When limited to adenocarcinomas, areas under the curve were 0.739 (95 % CI 0.642–0.835) for SUV_{max} and 0.555 (95 % CI 0.426–0.685) for tumor size. The optimum cutoff point among adenocarcinomas for SUV_{max} was 3.3, and the cutoff for tumor size was 5.0 cm. These results demonstrated that SUV_{max} was superior to tumor size in predicting nodal metastasis in NSCLC, particularly in adenocarcinoma.

Microscopic local tumor invasion, including the L, V, and PL factors and the lymph node metastasis was revealed by the tumor size (2 cm) and SUV_{max} (3.0) of the primary lesion (Table 3). When the tumor size was ≤2.0 cm ($n = 41$), the percentages of Ly1, V1–2, PL1–3, and pN1–3 were 12.2, 7.3, 4.9, and 17.1 %, respectively. The

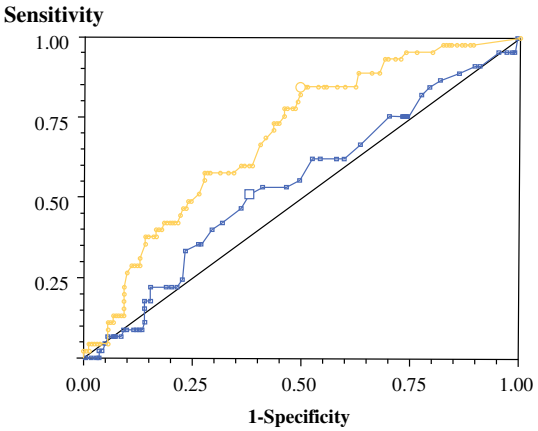

FIG. 1 Receiver operating characteristic (ROC) curves for maximum standardized uptake value (SUV_{max}; *yellow line*) and tumor size (*blue line*) for prediction of pathologic lymph node metastases in non-small-cell lung cancer (NSCLC). Area under the curve (AUC) was 0.693 (95 % CI 0.611–0.775) for SUV_{max} and 0.545 (95 % CI 0.449–0.641) for tumor size; this demonstrated the superior diagnostic accuracy of SUV_{max} compared to tumor size. The optimum cutoff point of each curve was 2.9 (*circles*) for SUV_{max} and 3.5 cm (*squares*) for tumor size

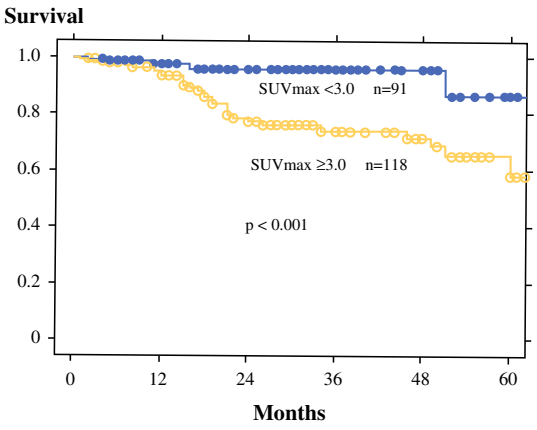

FIG. 2 Postoperative overall survival curves of patients with non-small-cell lung cancer (NSCLC) classified by the maximum standardized uptake value ($SUV_{max} < 3.0$ vs. ≥ 3.0). Survival in patients with $SUV_{max} < 3.0$ was better than survival in those with $SUV_{max} \geq 3.0$ ($p < 0.001$)

tumor size was not significant in the prediction of lymph node metastasis ($p = 0.4386$). When SUV_{max} was <3.0 ($n = 91$), the above percentages were 15.4, 3.3, 7.7, and 8.8 %; SUV_{max} was significantly associated with pathologically confirmed nodal metastases ($p < 0.0001$). Among 91 tumors with $SUV_{max} < 3.0$, the mean tumor size was 2.8 ± 1.5 cm (range 1.0–10.0 cm). Among these tumors, 32 (35.2 %) were ≤2.0 cm; however, 59 other tumors (64.8 %) were >2 cm in the longest dimension. Thus, we could identify more patients who could be resected with a low risk of local recurrence when SUV_{max} but not the tumor size, was used as a criterion for limited resection. Among 118 tumors with $SUV_{max} \geq 3.0$, the mean tumor size was 4.1 ± 2.0 cm (range 1.4–15.0), and 9 tumors (7.6 %) measured ≤2.0 cm.

When we classified patients with NSCLC according to the cutoff 3.0 for SUV_{max}, the postoperative 5-year overall survival rates were 86.6 % in patients with $SUV_{max} < 3.0$, and 58.1 % in patients with $SUV_{max} \geq 3.0$; this suggested that glucose uptake was closely associated with postsurgical survival ($p < 0.001$; Fig. 2). In contrast, 5-year overall survival rates were 93.5 % in patients with a tumor size ≤2 cm and 65.5 % in patients with a tumor size >2 cm, with no significant survival difference between the two groups ($p = 0.0867$).

DISCUSSION

Lung cancer mainly develops in the elderly population, particularly in heavy smokers. Because long-term smoking habits also cause chronic obstructive pulmonary disease and ischemic heart disease, the number of elderly lung cancer patients with poor cardiopulmonary function has increased in developed countries where there has been

TABLE 3 Relationship among tumor size, SUV_{max}, and microscopic tumor spread in pathologic specimens

Characteristic	Lymphatic invasion		Venous invasion		Pleural invasion		Lymph node metastasis	
	Ly0	Ly1	V0	V1–2	PL0	PL1–3	pN0	pN1–3
Tumor								
≤2 cm	36 (87.8 %)	5 (12.2 %)	38 (92.7 %)	3 (7.3 %)	39 (95.1 %)	2 (4.9 %)	34 (82.9 %)	7 (17.1 %)
>2 cm	96 (57.1 %)	72 (42.9 %)	111 (66.1 %)	57 (33.9 %)	126 (75.0 %)	42 (25.0 %)	130 (77.4 %)	38 (22.6 %)
p value	<0.001		<0.001		0.005		0.439	
SUV_{max}								
<3.0	77 (84.6 %)	14 (15.4 %)	88 (96.7 %)	3 (3.3 %)	84 (92.3 %)	7 (7.7 %)	83 (91.2 %)	8 (8.8 %)
≥3.0	55 (46.6 %)	63 (53.4 %)	61 (51.7 %)	57 (48.3 %)	81 (68.6 %)	37 (31.4 %)	81 (68.6 %)	37 (31.4 %)
p value	<0.001		<0.001		<0.001		<0.001	

SUV_{max} maximum standardized uptake value

rapid aging of the population. Therefore, organ-sparing surgery for lung cancer has become more important. Although sublobar resection appeared to be an option for such patients, a relatively high intrathoracic recurrence rate remains the most important problem that requires being resolved.[1] Dependable criteria for selecting patients suitable for intentional limited resection require to be identified. In this study, we found that SUV_{max} at the primary site determined by FDG-PET/CT was an indicator of NSCLC having low-grade locoregional invasiveness.

Originally, FDG-PET/CT did provide useful information about hilar and mediastinal nodal metastases in lung cancer. In a clinical study published in 2001, the sensitivity, specificity, and accuracy of CT and PET for detecting metastatic lymph nodes were 68, 61, 63, and 87, 91 and 82 %, respectively.[17] In advanced disease stages, differentiation between resectable N1/N2 disease and unresectable N3 disease could be performed reliably by PET/CT.[18] However, microscopic lymph node metastases are barely detected by PET/CT. In our present study, the sensitivity of PET/CT for pathologic lymph node metastasis was only 38 %. PET/CT staging of the mediastinum was less sensitive, particularly for elderly patients with early-stage NSCLC and in whom such staging had shown a lower PPV.[19] Other methods to determine the appropriate patients for limited resection are required.

Usually a tumor size of $\leq$2 cm has been used as a criterion for intentional limited resection in many institutions.[20–22] However, because the frequency of nodal metastases in this group was relatively high, lymph node dissection could not be safely omitted. For this reason, intraoperative pathologic examination of frozen sections from the sampled lymph nodes was recommended to exclude node-positive cases.[20,23] However, intraoperative pathologic examination is not always possible in every hospital, and intrapulmonary lymph nodes cannot be sampled in wedge resection cases at the lowest surgical risk in the highest risk patients. We believe that the most important factor is the biologic malignant potential of lung cancer rather than tumor size. Because SUV_{max} represents the physiologic proliferative activity of the tumor, we hypothesized that SUV_{max} could be used to select appropriate NSCLCs for limited resection. Recent studies have suggested the importance of SUV_{max} in the evaluation of biologic malignant potential of lung cancers. One study reported a low probability of lymph node involvement in NSCLCs <1 cm in size or with $SUV_{max} < 2.0$, which would allow the omission of the lymphadenectomy.[24] Our receiver operating characteristic analysis showed that a $SUV_{max} < 3.0$ was superior to a tumor size $\leq$2.0 cm for the prediction of tumors with pathologically negative lymph nodes. Our recent study demonstrated that SUV_{max} was closely associated with adenocarcinoma subtypes and postoperative survival.[25] As the percentage of area showing ground-glass opacities (GGO) in primary NSCLC lesions has been related to SUV_{max}, our results may support that high percentages of GGO lesions may be an indication for limited resection. An ongoing randomized trial (JCOG0802/WJOG4607L) comparing segmentectomy versus lobectomy for small-sized peripheral NSCLC tumors will provide useful information about the capabilities of limited resection.[26] In the microscopic infiltration of cancer cells around a primary lesion, a study analyzing 39 patients with NSCLC from stages I to IIIA found a strong correlation between SUV_{max} and the maximum linear distance from the tumor margin to the farthest extent of cancer cell spread in every dimension.[27] The mean distances measured by pathologic examination were 1.93, 3.90, and 9.60 mm for a SUV_{max} of $\leq$5, 5–10, and >10, respectively. In our present study, for the Ly, V, and PL factors, similar results were obtained in tumors $\leq$2 cm and in tumors with a $SUV_{max} < 3.0$. However, SUV_{max} (<3.0) could predict the absence of nodal involvement more reliably; <10 % of the cases were node-positive and more candidates 43.5 versus 19.6 % for limited resection. Statistically significant good postoperative survival in patients with a SUV_{max} of <3.0 supported the idea that this population may represent suitable candidates for sublobar resection. In practical applications of our suggested criterion of $SUV_{max} < 3.0$ for limited resection, both the tumor size (for assuring the safety resection margin) and preoperative lymph node status (for the assessment of metastases) should be carefully examined on a case-by-case basis.

In conclusion, SUV_{max} was more useful than tumor size for microscopically selecting less-invasive NSCLCs suitable for limited resection. Because pathologic node-positive cases were found only in 9 % patients when SUV_{max} at the primary site was <3.0, irrespective of the tumor size, organ-sparing limited resection, including wedge resection, could represent curative surgery for approximately 90 % in this patient group. These results should be verified by a well-designed prospective clinical study that examines a larger patient population.

CONFLICT OF INTEREST None.

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