Eur J Nucl Med Mol Imaging (2014) 41:2051–2057
DOI 10.1007/s00259-014-2831-6

ORIGINAL ARTICLE

# Metabolic parameters using $^{18}$F-FDG PET/CT correlate with occult lymph node metastasis in squamous cell lung carcinoma

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Received: 18 March 2014 / Accepted: 2 June 2014 / Published online: 3 July 2014


**Abstract**
*Purpose* The aim of this study was to investigate predictability of occult lymph node metastasis (OLM) using metabolic parameters on pretreatment $^{18}$F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/CT in squamous cell non-small cell lung carcinoma (SC-NSCLC) patients who were clinically node negative (cN0) before surgery.
*Methods* A total of 63 cN0 SC-NSCLC patients (M/F = 61/2, mean age 64.1±8.0) who underwent curative surgery with lymph node dissection were enrolled in this study. Metabolic tumor volume (MTV) of the primary tumor was obtained with a standardized uptake value (SUV) threshold of 2.5. Total lesion glycolysis (TLG) was calculated by multiplication of the MTV and its $SUV_{mean}$. Metabolic parameters ($SUV_{max}$, MTV, and TLG) and clinicopathological factors were analyzed for OLM.
*Results* Of 63 patients, 12 (19.0 %) had OLM. Significantly higher $SUV_{max}$, MTV, TLG, and pathological tumor size were observed in patients with OLM. The optimal cutoff values for prediction of OLM determined using a receiver-operating characteristic (ROC) curve were 8.8 for $SUV_{max}$, 18.9 $cm^3$ for MTV, 88.4 for TLG, and 2.8 cm for pathological tumor size. Univariate analysis showed correlation of $SUV_{max}$, MTV, and TLG with the rate of OLM. In multivariate analyses, high $SUV_{max}$ and MTV showed an association with an increased risk of OLM, after adjusting for age, sex, pathological tumor size, T stage, and location.
*Conclusion* Metabolic parameters on pretreatment $^{18}$F-FDG PET/CT were significant predictors for OLM in cN0 SC-NSCLC patients. Surgical planning can be tailored based on the parameters in order to reduce the risk of hidden residual lymph node metastases in patients.

**Keywords** Squamous cell lung carcinoma · Prediction · Occult lymph node metastasis · $^{18}$F-FDG PET/CT · Metabolic parameter

## Introduction

Lung cancer is the leading cause of cancer-related death worldwide and approximately 85~88 % of lung cancer is non-small cell lung cancer (NSCLC) [1]. Accurate initial staging for NSCLC patients is critical for selection of an optimal therapeutic plan, and complete surgical removal of all cancerous lesions is essential to cure the disease. The prevalence of occult lymph node metastasis (OLM) in NCSLC has been reported to be 14~19 %, and histological type, histological grade, primary tumor location, nodular type, tumor size, and maximum standardized uptake value ($SUV_{max}$) of $^{18}$F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) of primary tumor were reported as risk factors for OLM in patients with NSCLC [2–4]. Aggressive tailored management of NSCLC patients with high risk of OLM can improve clinical outcome by reducing

**Electronic supplementary material** The online version of this article (doi:10.1007/s00259-014-2831-6) contains supplementary material, which is available to authorized users.

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recurrence and mortality [5]. However, previous studies enrolled various pathological types of NSCLC, which can influence the results, and no study investigating presurgical risk factors predicting OLM only for clinical N0 (cN0) squamous cell non-small cell carcinoma (SC-NSCLC) patients has been reported. An appropriate surgical plan can be tailored to patients with high risk of OLM in order to reduce the chance of hidden residual lymph node metastases. Thus, accurate patient stratification for OLM in cN0 SC-NSCLC patients could lead to improved clinical outcomes.

$^{18}$F-FDG PET is widely used in management of lung cancer and is already an indispensable modality for evaluation of lymph node or distant metastasis [6–10]. The ability of $^{18}$F-FDG PET by direct assessment of each lymph node for the presence of metastasis is inherently limited; therefore, another approach to achievement of better accuracy in evaluation of lymph node metastasis of lung cancer is warranted. Several $^{18}$F-FDG PET studies have attempted to elucidate the predictive ability of $SUV_{max}$ for OLM in patients with NSCLC, and the results were generally promising [2–4, 11]. However, in previous studies, pathological type and status of disease staging were not stratified; therefore, the best cutoff of $SUV_{max}$ for prediction was variable. In addition, other metabolic PET parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), were not assessed as predictors.

Thus, the aim of the current study was to investigate predictability of OLM using metabolic parameters of $SUV_{max}$, MTV, and TLG on pretreatment $^{18}$F-FDG PET/CT exclusively for patients with cN0 SC-NSCLC.

## Materials and methods

### Patients

We conducted an analysis of 63 patients with previously untreated, biopsy-proven SC-NSCLC from January 2006 to December 2011 whose medical records were retrieved from the cancer registry at Kyungpook National University Hospital. Eligibility criteria for participation were no FDG uptake in mediastinal and hilar lymph nodes on $^{18}$F-FDG PET/CT. Patients who showed evidence of distant metastatic disease or who received preoperative chemotherapy or radiation therapy were excluded from the study. All patients had undergone primary tumor resections and lymph node dissections.

### $^{18}$F-FDG PET/CT acquisition protocol

All patients fasted for at least 6 h, and blood glucose levels were checked before administration of $^{18}$F-FDG. Examinations were rescheduled for patients with elevated blood glucose levels, and their blood glucose concentration was managed in order to achieve a level of less than 150 mg/dl. Approximately 8.1 MBq of $^{18}$F-FDG per kilogram of body weight was injected intravenously, and patients were advised to rest for 1 h before acquisition of the PET/CT image. PET/CT scans were performed using a Reveal RT-HiREZ 6-slice CT scanner (CTI Molecular Imaging, Knoxville, TN, USA) and a 16-slice CT Discovery STE scanner (GE Healthcare, Milwaukee, WI, USA). Before the PET scan, for attenuation correction, a low-dose CT scan was acquired without contrast enhancement from the skull base to the thigh, with the patient supine and breathing quietly. PET scans with a maximum spatial resolution of 6.5 mm (Reveal PET/CT) and 5.5 mm (Discovery PET/CT) were also obtained from the skull base to the thigh, for 3 min per bed position. PET images obtained using the Reveal PET/CT and Discovery PET/CT scanners were reconstructed with a 128×128 matrix, an ordered subset expectation maximum iterative reconstruction algorithm (four iterations, eight subsets), a Gaussian filter of 5.0 mm, and a slice thickness of either 3.0 mm (Reveal PET/CT) or 3.27 mm (Discovery PET/CT).

### Image analysis

PET/CT images were reviewed by an experienced nuclear medicine physician who was unaware of the clinical findings. Semiquantitative and volumetric analyses of the primary tumor were performed using the volume viewer software on a GE Advantage Workstation 4.3 (GE Healthcare, Milwaukee, WI, USA). $SUV_{max}$ was calculated using the following formula:

$$\mathrm{SUVmax} = \frac{\text{maximum activity in region of interest}\left(\mathrm{MBq}\middle/\mathrm{g}\right)}{\text{injected dose}(\mathrm{MBq})\middle/\text{body weight}(\mathrm{g})}$$

We used the automatic method for delineation of the volume of interest using an isocontour threshold method based on SUV. An automatic autocontouring process with an SUV threshold of 2.5 was used to define the volume of interest. TLG was calculated by multiplication of MTV and its $SUV_{mean}$.

### Surgical resection and pathological examination

All surgical resections and mediastinal lymph node dissections were performed by thoracic surgeons at Kyungpook National University Hospital. Resected tumor tissue and lymph nodes were examined by a pulmonary histopathologist for the presence or absence of malignancy using standard techniques and immunohistochemical staining was also performed at the pathologist's discretion. Central location was where the center of mass was within the hilar structures, and noncentral location was where the center of mass was within

the parenchyma and with no or minimal contact with hilar structures.

### Statistical analyses

Continuous data were expressed as mean±standard deviation; categorical data were presented as frequency and percentage. Continuous data analysis was performed using the Mann–Whitney U test and categorical data were calculated using Pearson's chi-square test. Receiver-operating characteristic (ROC) analysis was performed for determination of an optimal cutoff of primary tumor $SUV_{max}$, MTV, and TLG for prediction of OLM. The odds ratio test was used for comparison of the equality of the presence of OLM according to each variable. Logistic regression was used for multivariate analyses. Statistical analysis was performed using MedCalc software (Windows XP, version 12.3, Mariakerke, Belgium). A $p$ value of less than 0.05 was considered statistically significant.

## Results

### Patients' characteristics

Our cohort consisted of 61 men (96.8 %) and 2 women (3.2 %). The average age of the subjects was 65.0±8.0 years, ranging from 45 to 79 years. Surgical resection was performed at 10.3±8.2 days after acquisition of $^{18}$F-FDG PET/CT and OLM was found in 12 (19.7 %) of 63 patients. Nine patients were pathological N1 stage and three patients were pathological N2 stage. Location, tumor size, and pathological T staging were statistically different between patients with OLM and those without ($p$=0.027, 0.043, and 0.013, respectively) (Table 1). No differences in age, sex, tumor site, and histological grade were observed between patients with OLM and those without. Demographic data of the 63 patients are shown in Table 1. Significantly higher $SUV_{max}$, MTV, and TLG were observed in patients with OLM (Table 2).

### Receiver-operating characteristic curve analysis

The ability of $SUV_{max}$, MTV, and TLG of the primary tumor to predict OLM was depicted by the ROC curve. The optimal cutoff values of 8.8 for $SUV_{max}$ (sensitivity 91.7 %, specificity 52.9 %, area under the ROC curve (AUC) 0.712, $p$=0.005), 18.9 $cm^3$ for MTV (sensitivity 83.3 %, specificity 66.7 %, AUC 0.758, $p$=0.001), and 88.4 for TLG (sensitivity:83.3 %, specificity 66.7 %, AUC 0.737, $p$=0.003) were determined using ROC curve analysis. In addition, the cutoff value of 28 mm for tumor size (sensitivity 83.3 %, specificity 52.9 %, AUC 0.689, $p$=0.029) was also determined using ROC curve analysis (Supplementary Fig. 1). Consequently, $SUV_{max}$, MTV, and TLG were examined as prognostic parameters for prediction of OLM. The ROC curve showed that MTV (AUC 0.758) had a better predictive performance than $SUV_{max}$ (AUC 0.712) and TLG (AUC 0.737) for prediction of OLM.

### Univariate analysis for prediction of OLM in cN0 SC-NSCLC

Univariate analysis was performed for determination of correlation with OLM (Table 3). We observed a significantly higher rate of OLM for patients with $SUV_{max}$ of >8.8 compared to those with $SUV_{max}$ of ≤8.8 ($p$=0.020). A significantly higher rate of OLM was observed for patients with MTV of >18.9 $cm^3$ compared to patients with MTV of ≤18.9 $cm^3$ ($p$=0.006). A significantly higher rate of OLM was observed for patients with TLG of >88.4 compared to patients with TLG of ≤88.4 ($p$=0.008). In addition, patients with tumor size >28 mm had a significantly higher rate of OLM than patients with tumor size ≤28 mm ($p$=0.036). Patients with central location had a significantly higher rate of OLM than patients with noncentral location ($p$=0.036). Age, sex, tumor site, histological grade, and pathological T stage did not show correlation with OLM.

### Multivariate analysis for prediction of OLM in cN0 SC-NSCLC

By multivariate analyses after adjusting for age, sex, pathological tumor size, T stage, and location (Table 4), $SUV_{max}$ and MTV were significant parameters in prediction of OLM [odds ratio 9.84, 95 % confidence interval (CI) 1.04–93.53, $p$=0.047 and odds ratio 20.65, 95 % CI 1.09–389.87, $p$=0.043, respectively]. TLG did not reach statistical significance (odds ratio 13.71, 95 % CI 0.76–246.07, $p$=0.076).

## Discussion

In the current study, we demonstrated that the $SUV_{max}$ and MTV, as determined by $^{18}$F-FDG PET/CT, are statistically significant predictors for OLM in patients with cN0 SC-NSCLC after adjusting for clinicopathological factors. According to our findings, patients with $SUV_{max}$ >8.8 and MTV >18.9 $cm^3$ had a significantly higher rate of OLM.

In early SC-NSCLC, pulmonary lobectomy with lymph node dissection is the standard surgery and the majority of cN0 SC-NSCLC shows a good prognosis after surgery [3]. However, several studies have suggested that OLM might be a major cause of local recurrence and related to a poor prognosis after surgical resection in cN0 NSCLC [5, 11]. Lymph node analysis will improve the staging of tumors and may contribute to the finding of improved survival by means of stage migration [12]; however, extensive nodal analysis may induce

**Table 1** Demographic data

| Characteristics | Total ($n$=63) | OLMN ($n$=51) | OLMP ($n$=12) | $p$ value |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Mean age (years) | 64.1±8.0 | 64.5±7.7 | 62.5±9.5 | 0.446[a] |
| Sex | | | | |
| Male | 61 | 49 | 12 | 0.569 |
| Female | 2 | 2 | 0 | |
| Pathological characteristics | | | | |
| Tumor site | | | | |
| RUL | 14 | 13 | 1 | 0.352 |
| RML | 3 | 3 | 0 | |
| RLL | 18 | 15 | 3 | |
| LUL | 17 | 13 | 4 | |
| LLL | 11 | 7 | 4 | |
| Location | | | | |
| Central | 34 | 24 | 10 | 0.027 |
| Noncentral | 29 | 27 | 2 | |
| Tumor size (mm) | 32.4±15.9 | 29.6±11.8 | 44.5±24.5 | 0.043[a] |
| Histological grade | | | | |
| Well differentiated | 4 | 3 | 1 | 0.949 |
| Moderately differentiated | 54 | 44 | 10 | |
| Poorly differentiated | 5 | 4 | 1 | |
| Pathological T stage | | | | |
| T1 | 28 | 24 | 4 | 0.013 |
| T2 | 31 | 26 | 5 | |
| T3 | 4 | 1 | 3 | |

*OLMN* occult lymph node metastasis negative, *OLMP* occult lymph node metastasis positive, *RUL* right upper lobe, *RML* right middle lobe, *RLL* right lower lobe, *LUL* left upper lobe, *LLL* left lower lobe

[a] Mann–Whitney U test

adverse effects [13]. Video-assisted thoracoscopic surgery is being used in the surgical resection of most lung cancers, and pathological N1 patients with cN0 NSCLC might need bilobectomy, sleeve lobectomy, or double sleeve lobectomy instead of usual lobectomy [4, 14]. Therefore, identification of potential OLM predictors and selection of high-risk patients for OLM in cN0 patients are urgently needed. We believe that the results of the current study would be helpful in surgical planning to reduce the chance of hidden residual lymph nodes.

$^{18}$F-FDG uptake was identified as a significant prognostic factor related to OLM in patients with NSCLC [2–4]. Miyasaka et al. reported that an $SUV_{max}$ of the primary tumor >10 was a significant predictor of pathological nodal involvement and poor prognosis in patients with NSCLC [4]. Park et al. reported that an $SUV_{max}$ of the primary tumor >7.3 was an independent predictor of OLM in patients with clinical stage IA NSCLC [2]. Li et al. reported that an $SUV_{max}$ of the primary tumor >4.3 was an independent predictor of OLM in patients with clinical N0 NSCLC [3]. In these previous studies, subjects with heterogeneous histological types and TNM stages were included, and the homogeneity of subjects could have a significant effect on the cutoff value of $SUV_{max}$. In the current study, only patients with cN0 SC-NSCLC were enrolled and $SUV_{max}$ of the primary tumor was a significant predictor for OLM in patients. In the current study, the most discriminative cutoff value of the primary

**Table 2** Metabolic PET parameters

| Variables | OLMN ($n$=51) | OLMP ($n$=12) | $p$ value[a] |
|---|---|---|---|
| $SUV_{max}$, median (95 % CI) | 8.8 (7.9–11.1) | 12.7 (9.2–17.7) | 0.023 |
| MTV ($cm^3$), median (95 % CI) | 14.5 (8.8–18.4) | 28.5 (20.1–177.7) | 0.006 |
| TLG, median (95 % CI) | 65.3 (38.4–88.2) | 139.8 (94.2–1097.2) | 0.011 |

*OLMN* occult lymph node metastasis negative, *OLMP* occult lymph node metastasis positive, *$SUV_{max}$* maximum standardized uptake value, *CI* confidence interval, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

[a] Mann–Whitney U test

**Table 3** Univariate analyses for prediction of OLM in cN0 patients with SC-NSCLC

| Variables | Cutoff | Occult metastasis (%) | Odds ratio | 95 % CI | *p* value[a] |
|---|---|---|---|---|---|
| Age (years) | ≤65<br>>65 | 7/33 (21.21)<br>5/30 (16.67) | 0.74 | 0.21–2.65 | 0.647 |
| Sex | Male<br>Female | 12/61 (19.67)<br>0/2 (0) | 1.05 | 0.47–23.25 | 0.975 |
| Tumor size | ≤28 mm<br>>28 mm | 2/29 (6.90)<br>10/34 (29.41) | 5.63 | 1.12–28.27 | 0.036 |
| Tumor site | Upper & middle lobe<br>Lower lobe | 5/34 (14.7)<br>7/29 (24.1) | 1.85 | 0.52–6.60 | 0.346 |
| Location | Noncentral<br>Central | 2/29 (6.9)<br>10/34 (29.4) | 5.63 | 1.12–28.27 | 0.036 |
| Histological grade | Well & moderately differentiated<br>Poorly differentiated | 11/58 (19.0)<br>1/5 (20.0) | 1.07 | 0.11–10.52 | 0.955 |
| Pathological T stage | T1<br>T2-3 | 4/28 (14.29)<br>8/35 (22.86) | 1.78 | 0.47–6.66 | 0.393 |
| SUVmax | ≤8.8<br>>8.8 | 1/28 (3.57)<br>11/35 (31.43) | 12.38 | 1.49–103.07 | 0.020 |
| MTV ($cm^3$) | ≤18.9 $cm^3$<br>>18.9 $cm^3$ | 2/36 (5.56)<br>10/27 (37.04) | 10.00 | 1.97–50.84 | 0.006 |
| TLG | ≤88.4<br>>88.4 | 2/35 (5.71)<br>10/28 (35.71) | 9.17 | 1.81–46.47 | 0.008 |

*CI* confidence interval, *$SUV_{max}$* maximum standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

[a] Odds ratio test

tumor $SUV_{max}$ for prediction of OLM was 8.8. The cutoff value of $SUV_{max}$ was higher compared to those of previous studies, and it might arise due to differences among enrolled subjects. The histological types of NSCLC can greatly influence the value of $SUV_{max}$. The high cutoff value of $SUV_{max}$ in the current study appears to be caused by a higher $SUV_{max}$ of SC-NSCLC compared to lung adenocarcinoma [15].

In clinical practice, $SUV_{max}$ is most commonly used as a metabolic parameter due to feasible measurement; however, it has vulnerable points as well. First, $SUV_{max}$ can be biased toward many sources, including body composition and habitus, length of FDG uptake period, plasma glucose, recovery coefficient, tumor volume, and volume of interest [16]. Second, $SUV_{max}$ is merely a single-voxel value representing the most intense $^{18}$F-FDG uptake in the tumor; it is known to be affected by noise, partial volume effect, and image resolution [17, 18]. Therefore, $SUV_{max}$ may not be the best surrogate marker representing the metabolic status of the tumor, and other metabolic parameters are needed as better markers than the $SUV_{max}$ [19].

Assessment of tumor volume is an important feature of cancer therapeutics. Tumors do not always have a uniform shape and a homogeneous composition; therefore, anatomical imaging might result in erroneous tumor volume in heterogeneous tumors. Fortunately, the nonviable and nontumorous tissues within the tumor do not take up $^{18}$F-FDG; therefore, the metabolic volumetric information obtained with $^{18}$F-FDG PET should be more accurate than tumor volumes measured using anatomical images [19]. With advances of image analysis tools, metabolic volumetric assessment can be performed feasibly and consistently, with no interobserver variability, and could potentially be applied routinely in clinical practice [20].

To the best of our knowledge, no study showing that metabolic volumetric parameters on pretreatment $^{18}$F-FDG PET are independent predictors of OLM in patients with

**Table 4** Multivariate analysis for prediction of OLM in patients with cN0 SC-NSCLC after adjusting for age, sex, pathological tumor size, T stage, and location

| Variable | Cutoff | Odds ratio | 95 % CI | *p* value[a] |
|---|---|---|---|---|
| $SUV_{max}$ | ≤8.8 vs >8.8 | 9.84 | 1.04–93.53 | 0.047 |
| MTV ($cm^3$) | ≤18.9 $cm^3$ vs >18.9 $cm^3$ | 20.65 | 1.09–389.87 | 0.043 |
| TLG | ≤88.4 vs >88.4 | 13.71 | 0.76–246.07 | 0.076 |

*CI* confidence interval, *$SUV_{max}$* maximum standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

[a] Binary logistic regression

NSCLC has been reported. In the current study, we found that cN0 SC-NSCLC patients with an MTV greater than 18.9 $cm^3$ showed 19.79-fold higher prevalence of OLM than patients with an MTV less than the value. In order to obtain MTV, segmentation of primary tumor is necessary. Although primary tumor can be defined by various methods, such as gradient-based threshold, background threshold, and percentage threshold approaches, there is as yet however no standardized method for the segmentation. In this study, MTV was defined as primary tumor volume segmented by a fixed threshold SUV of 2.5 and it demonstrated better results than the volume segmented with a fixed threshold SUV of 3.0, fixed percentage of 40 or 50 %, for predicting OLM (data not shown) [19, 21].

TLG, a composite parameter representing both tumor volume and tumoral metabolic activity, which is determined by multiplying tumor volume derived from $^{18}$F-FDG PET/CT by an average SUV, was higher in subjects with OLM and also predicted OLM by univariate analysis. However, TLG had a smaller AUC value than MTV and did not reach statistical significance in multivariate survival analysis. From the results for MTV and TLG, MTV appears to be a better predictor than TLG for OLM in patients with cN0 SC-NSCLC.

In univariate analysis, the metabolic parameters obtained on $^{18}$F-FDG PET/CT ($SUV_{max}$, MTV, and TLG) were stronger predictors than clinicopathological parameters for prediction of OLM in patients with cN0 SC-NSCLC. In multivariate analysis of metabolic PET parameters, by adjusting for the clinicopathological predictors, MTV and $SUV_{max}$ were significant predictors for OLM and the MTV was the strongest predictor. Based on the results, intensive node dissection might be helpful to cN0 SC-NSCLC patients with a high MTV, due to the high prevalence of OLM, which was not visualized on all imaging studies.

Our study has several limitations. First, because it used a retrospective cohort, it was subject to multiple biases, most importantly a selection bias. Second, we studied a relatively small number of patients. Third, two types of PET scanner were used for the study, which might affect values of metabolic PET parameters. Performance of a larger, multi-institutional prospective randomized study is needed for further validation of the current results.

## Conclusion

Metabolic parameters on pretreatment $^{18}$F-FDG PET/CT were significant predictors for OLM in patients with cN0 SC-NSCLC. Therefore, surgical planning might be tailored according to the PET results and intensive node dissection can be helpful in patients with high metabolic parameters.

**Acknowledgments** This work was supported by grants (A111345) from the Korea Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea; a grant from the National Nuclear R&D Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (No.2012M2A2A7014020); a grant from the National Research Foundation of Korea (NRF) grant funded by the Korean government (MEST) (No.2009-0078222, 2009-0078234); a grant from the Medical Cluster R&D Support Project of Daegu Gyeongbuk Medical Innovation Foundation, Republic of Korea (2013).

**Conflicts of interest** None.

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