RESEARCH ARTICLE

# FDG PET-CT in Non-small Cell Lung Cancer: Relationship between Primary Tumor FDG Uptake and Extensional or Metastatic Potential

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## Abstract

**Objective: To explore the relationships between primary tumor $^{18}$F-FDG uptake measured as the SUVmax and local extension, and nodal or distant organ metastasis in patients with NSCLC on pretreatment PET-CT. Methods: 93 patients with NSCLC who underwent $^{18}$F-FDG PET-CT scans before the treatment were included in the study. Primary tumor SUVmax was calculated; clinical stages, presence of local extension, nodal and distant organ metastases were recorded. The patients with SUVmax≥2.5 were divided into low and high SUVmax groups by using the median SUVmax. The low SUVmax group consisted of 45 patients with SUVmax<10.5, the high SUVmax group consisted of 46 patients with SUVmax≥10.5. Their data were compared statistically. Results: 91 cases with SUVmax≥2.5 were included for analysis. The mean SUVmax in patients without any metastasis was 7.42±2.91 and this was significantly lower than that (12.18±4.94) in patients with nodal and/or distant organ metastasis (*P*=0.000). In the low SUV group, 19 patients had local extension, 22 had nodal metastasis, and 9 had distant organ metastasis. In the high SUV group, 31 patients had local extension, 37 had nodal metastasis, and 18 had distant organ metastases. There was a significant difference in local extension (*P* =0.016), distant organ metastasis (*P* =0.046), and most significant difference in nodal metastasis rate (*P* =0.002) between the two groups. In addition, there was a moderate correlation between SUVmax and tumor size (r = 0.642, *P*<0.001), tumor stage (r = 0.546, *P*<0.001), node stage (r = 0.388, *P*<0.001), and overall stage (r = 0.445, *P*= 0.000). Conclusion: Higher primary tumor SUVmax predicts higher extensional or metastatic potential in patients with NSCLC. Patients with higher SUVmax may need a close follow-up and more reasonable individual treatment because of their higher extensional and metastatic potential.**

**Keywords:** Non-small cell lung cancer - FDG-PET - SUV - clinical staging - metastasis

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## Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with nearly 1.4 million deaths each year (Jemal et al., 2010). Of the 1.6 million new cases of lung cancer diagnosed each year, approximately 220,000 are diagnosed in the United States (Jemal et al., 2010). Non-small cell lung cancers (NSCLC) accounts for about 85% of lung cancers (Ramalingam et al., 2011), in which adenocarcinoma is the most common histopathological type in recent decades (Ladanyi et al., 2008). Unfortunately, despite advancements in this field, treatment outcomes have not improved obviously over the last 30 years. Metastases and post-surgical recurrence of the primary tumor are the major cause of death due to NSCLC patients.

In patients with NSCLC, accurate staging, especially nodal staging is very important in decision making for treatment and predicting outcome (Felip et al., 2005; Detterbeck et al., 2009). However, patients belonging to the same stage can have different outcomes, despite being with the same treatment (Birim et al., 2006). Therefore, other useful prognostic factors, specifically predictors that can be assessed via noninvasive examination in a routine clinical setting, are needed to guide decisions regarding risk-adapt treatment strategies.

$^{18}$F-fluorodeoxyglucose positron emission tomography–computed tomography ($^{18}$F-FDG PET-CT), which provides morphological and metabolic data of malignancy, has become an important non-invasive tool for the staging as well as for the assessment of the primary tumor and distant metastasis in NSCLC (Lardinois et al., 2003; Ung et al., 2007). FDG uptake in the primary tumor measured as the maximum standardized uptake

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value (SUVmax) by PET, which well known measure indicating the disease activity or the aggressiveness of tumor (Higashi et al., 2005; Hellwig et al., 2007; Takenaka et al., 2009), can be easily obtained and is the most widely used parameter for the analysis of $^{18}$F-FDG PET images in clinical practice. As we all known, metastasis occurs primary by dissemination not only through the lymphatic and blood vessels but local extension in NSCLC. However, few studies have evaluated the relationship between the primary tumor SUVmax and local extension in patients with NSCLC.

In this study, the relationship between FDG uptakes within the primary tumor using SUVmax and local extension, lymph node or distant organ metastasis in NSCLC patients who underwent $^{18}$F-FDG PET-CT for staging before initial treatment was assessed retrospectively.

## Materials and Methods

*Clinical data*

We retrospectively analyzed the $^{18}$F-FDG PET-CT findings of 93 consecutive newly diagnosed NSCLC patients with the mean age of 59 years (range, 31-82 years), between June 2008 and May 2011. There were 57 (61.3%) males, mean age 58.6 years (range, 38-82 years) and 36 (38.7%) females, mean age 58.7 years (range, 31-73 years). All patients were defined by histological or cytological evidences. Of all the patients, 52 patients underwent surgical resection and the rest were non-operative. The patients were referred to the number nuclear medicine department for initial staging with PET-CT scan before treatment. Histological diagnosis of the tumors was based on the criteria of the World Health Organization (Gibbs et al., 2001) and the tumor-node metastasis (TNM) stage was determined according to revised criteria (Goldstraw et al., 2007).

*FDG PET-CT imaging*

$^{18}$F-FDG PET-CT scans were performed with a whole-body PET-CT scanner (Discovery LS PET-CT system; GE Healthcare Medical Systems, Bucks, U.K.). All patients had been fasting for at least 6 hours before PET imaging, and serum glucose levels were measured to ensure that the results were<6.0 mmol/L. After intravenous injection of 5.0 MBq/kg $^{18}$F FDG, the patients were then kept at rest in a quiet room for at least 50 minutes. Then PET-CT scanning was performed from the skull to the thighs. In general, the spiral CT component was performed with an x-ray tube voltage peak of 140 kv, 90 mA, a 0.75:1 pitch, a slice thickness of 5.0 mm, and a rotation speed of 7.5seconds per rotation. A PET scan was acquired for six to seven bed positions, and each position lasted 4.0 min in a two dimensional mode. A full-ring dedicated PET scan of the same axial range followed. PET images were reconstructed with CT-derived attenuation correction using the ordered-subset expectation maximization software.

*Imaging Analysis*

The PET-CT images were reviewed using the automatic PET-CT fusion software on the workstation. A volumetric region-of-interest (ROI) around the outline of primary tumor in the NSCLC was placed on the axial PET images using the semi-automatic software. A threshold of 40% of the maximum signal intensity was selected to delineate ROI. Then SUVmax, SUVmean and tumor volume (TV) were automatically calculated by the PET-CT fusion software and these values were recorded from the workstation. Both radiologists who conducted the measurements together were blinded to the clinical details. We used the SUVmax in the ROI (Ikushima et al., 2010) and SUVmax of 2.5 as cut-off (Ma et al., 2006) to eliminate partial volume artifacts in SUVmax measurement. After applying the cut-off, a final total of 91 cases were included for analysis as SUVmax in 2 patients was less than 2.5.

*Statistical analysis*

Statistical analysis was done using SPSS 17.0 (Chicago, Illinois, USA). The mean of the measurement data was expressed as mean±standard deviation (mean±S.D). The differences in local extension, lymph node and distant organ metastases between the low and the high SUV groups were compared using chi-square test. The difference of the primary tumor SUVmax values between lymph node positive and negative cases was compared using an unpaired t-test. An evaluation was made of the linear relationship between tumor size, tumor stage, nodal stage, and overall stages of the patients and their SUVmax using Spearman's correlation. *P* values less than 0.05 were considered significant.

## Results

The SUVmax ranged from 2.8 to 26.6 (mean 10.77±4.93). The median SUVmax was 10.5, the low SUVmax group ranged from 2.8 to 10.3 (mean 6.94±2.01), and the high SUVmax group ranged from 10.5 to 26.6 (mean14.51±3.96). The clinical characteristics of patients in the low and high group are seen in Table 1

The mean SUVmax in patients without any metastasis on $^{18}$F-FDG PET-CT was 7.42±2.91 and this was significantly lower than the mean SUVmax (12.18±4.94) in patients with lymph node and/or distant organ metastasis (*P*=0.000) (Figure 1).

Local extension, lymph node, and distant organ metastasis in the low and high group were seen in table 2. Local extension including primary tumor invasion to the main bronchus, visceral pleura, chest wall, mediastinum,

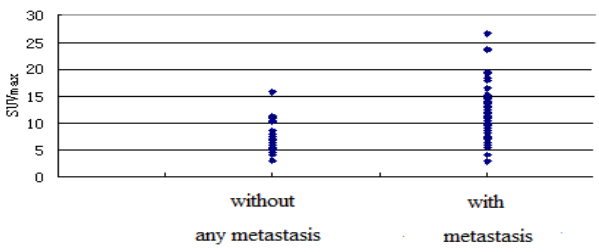


**Figure 1. Scattergram of SUVmax of NSCLC in Group Without Any Metastasis and the Group with Lymph Node and/or Distant Organ Metastasis**

**Table 1. Clinical Characteristics of Patients (n=91)**

| Characteristics | No. of patients | |
|---|---|---|
| | Low SUVmax group (SUVmax<10.5) | High SUVmax group (SUVmax ≥10.5) |
| Age (31–82 years) | | |
| < 59 years | 23 | 21 |
| ≥ 59years | 22 | 25 |
| Sex | | |
| Male | 26 | 30 |
| Female | 19 | 16 |
| Histology | | |
| Squamous | 6 | 18 |
| Adenocarcinoma | 38 | 25 |
| Adenosquamous | 1 | 3 |
| Tumor location | | |
| Left upper lobe | 12 | 15 |
| Left lower lobe | 7 | 9 |
| Right upper lobe | 12 | 13 |
| Right middle lobe | 1 | 3 |
| Right lower lobe | 13 | 6 |
| AJCC/UICC TNM stage | | |
| IA | 14 | 0 |
| IB | 8 | 4 |
| IIA | 7 | 3 |
| IIB | 0 | 5 |
| IIIA | 3 | 12 |
| IIIB | 4 | 4 |
| IV | 9 | 18 |
| CEA(mg/L) | | |
| ≤ 5.0 | 23 | 23 |
| > 5.0 | 22 | 23 |

**Table 2. Summary of Local Extension, Lymph Node, and Distant Organ Metastases**

| | Low SUVmax group (45 patients with SUVmax<10.5) | High SUVmax group (46 patients with SUVmax≥10.5) | *P* value |
|---|---|---|---|
| Local extension (%) | 19 (42.2%) | 31 (67.4%) | 0.016 |
| Lymph node metastasis (%) | 22 (48.9%) | 37 (80.4%) | 0.002 |
| Distant organ metastasis (%) | 9 (20%) | 18 (39.1%) | 0.046 |

and recurrent laryngeal nerve, etc were seen in 19 patients (42.2%) in the low SUVmax group and 31 patients (67.4%) in the high SUVmax group ($P = 0.016$). Lymph node and distant organ metastases were more frequent in the high SUVmax (80.4%, 37/46; 39.1%, 18/46) than that of the low SUVmax group (48.9%, 22/45; 20%, 9/45), ($P = 0.002$; $P = 0.046$).

In addition, Spearman's rank correlation showed a significant association of SUVmax of primary tumor with tumor size, tumor stages, nodal stages, and overall stages of the patients (Table 3).

**Table 3. Correlation Between SUVmax and Tumor Size or Tumor Stage**

| | Correlation coefficient | *P*-value |
|---|---|---|
| Tumor diameter | 0.642 | *P*<0.001 |
| Tumor stage | 0.546 | *P*<0.001 |
| Node stage | 0.388 | *P*<0.001 |
| Overall stage | 0.445 | *P*=0.000 |

## Discussion

$^{18}$F-FDG PET-CT has been increasingly used for staging, treatment response assessment and therapy planning in NSCLC (Huang et al., 2011; Li et al., 2012 ) since it was introduced into clinical practice in 1998 (De Wever et al., 2009). Apart from qualitative assessment in the detection of metastases, PET-CT provides the opportunity of a semi-quantitative measure of tumor glycolysis using SUV. SUVmax is the highest SUV measurement in the ROI and is the most commonly used measurement in clinical practice because of its being least affected by partial volume effects (Ikushima et al., 2010). SUVmax is also defined as a unique noninvasive method for studying biochemical and metastatic changes in cancer tissues (Gambhir, 2002). The relationship between SUVmax of primary tumor and local extension, lymph node and distant organ metastasis was investigated.

Our results showed that the likelihood of lymph node and distant organ metastasis increases with increasing primary tumor SUVmax in patients with NSCLC. In addition, the results showed local extension of the primary tumor such as the main bronchus, visceral pleura, chest wall, or mediastinum were more frequent in the high SUVmax group than in the low SUVmax group, and that it has not yet been reported.

SUVmax has been correlated with tumor proliferation rate, tumor grade, and expression of glucose transporters, which are biomarkers in various types of malignant tumors (Takenaka et al., 2009; Taylor et al., 2009; Park et al., 2012). Metastasis is the major cause of death due to several malignancies, including NSCLC and it occur primary by dissemination through the lymphatic and blood vessels. Nambu et al. (2009) have reported that the likelihood of lymph node metastasis increases with increase of SUVmax of the primary tumor in patients with NSCLC. Our results are consistent with their observations. In their study, they also added when the SUVmax of the primary tumor is greater than 12, the probability of lymph node metastasis is high, reaching 70%, irrespective of the degree of FDG accumulation into the lymph node stations. This finding would allow us to more sensitively predict the presence of lymph node metastases, including microscopic ones that cannot be detected by a direct evaluation of the lymph node stations.

Higashi et al. (2005) have reported in a multicenter study that the incidence of lymphatic vessel invasion and lymph node metastasis in NSCLC depended on $^{18}$F-FDG uptake of the primary tumor and concluded that $^{18}$F-FDG uptake by the primary tumor is a strong predictor of lymphatic vessel invasion and lymph node metastasis. Similarly, Li et al. (2009) reported that the SUVmax of primary tumor is a potential indicator of metastases in T1 stage NSCLC. These findings may be explained by the fact that the greater the FDG uptake is, the higher is the malignant grade. In our study, local extension, and nodal or distant organ metastasis rate was higher in patients with high SUVmax.

In our study, we have also shown that the average of SUVmax was significantly lower in patients without any metastasis than that with lymph node and/or distant organ metastasis. These results further suggested that SUVmax may in partly reflect the potential of metastasis in primary

tumor in NSCLC and are in line with other studies (Li et al., 2009; Nambu et al., 2009). However, there was no upper threshold of SUVmax of NSCLC, above which lymph node and/or distant organ metastasis were always present. Thus, even when a primary tumor in NSCLC shows high SUVmax exceeding 10 or 20, the presence of lymph node and/or distant organ metastasis is still inconclusive based on the evaluation of the SUVmax of the primary tumor.

The universally accepted TNM staging system is the most important prognostic factor from NSCLC (Sculier et al., 2008). We believe that, and we also have shown that there are moderate correlations between the primary tumor SUVmax with tumor size, tumor stage, nodal stage, and overall stage. These results suggested that SUVmax in partly reflect the comprehensive information, such as tumor size, local extension, lymph node and/or distant organ metastasis within the TNM staging system. They also further prove the prognostic significance of primary tumor SUVmax in NSCLC. However, its mechanism remains uncertain and it is also controversial whether the SUVmax of primary tumor predict prognosis in patients with NSCLC independent of the TNM staging system.

In our study, 52 patients underwent surgical resection and 8 patients with the PET-CT interpreted as positive for mediastinal nodes were negative confirmed by postoperative pathologic results. Iskender et al. (2012) thought that metastasis into the mediastinal lymph nodes occurred in false-negative patients of NSCLC staged with PET-CT in theory. At the same time, they also shown that false-positivity of mediastinal lymph nodes has negative effect on survival in potentially resectable NSCLC patients staged with PET-CT. On the one hand, in response to the antigenity of tumor cells, regional lymph nodes may initiate and develop complex immune reactions. Acting as efficient barriers, the lymph nodes may be able to destroy invading tumor cells completely, or at least stop their dissemination temporarily (Ioachim et al., 2009). So we could not detect metastasis histopathologically because tumor cells were already destroyed in the lymph nodes. In another theory, metastasis was in the early stage in these false-positivity lymph nodes and we could not detect metastasis with routine histopathological examination.

Although pathological findings served as the gold standard of extension and metastasis, it has been found in many literatures (Pauls et al., 2007; Chao et al., 2012; Cuaron et al., 2012) that integrated $^{18}$F-FDG PET-CT scans is the best noninvasive imaging technique for the accurate staging of local tumor extent, mediastinal lymphnode involvement, and distant metastatic disease in NSCLC. Especially for the non-operative patients with NSCLC, $^{18}$F-FDG PET-CT is more accurate than CT alone, PET alone (Lardinois et al., 2003; Fischer et al., 2006), and has become a standard test in evaluating the clinical TNM status (De Wever et al., 2007).

Follow-up duration of the patients after initial $^{18}$F-FDG PET-CT was not long enough in our study to evaluate the relationship between the primary tumor SUVmax and survival. To our knowledge, there have been no published randomized clinical trials regarding the topic that increased metabolic activity of primary tumor suggested to achieve better survival until now. Despite the measurement of SUVmax in the PET imaging affected by several factors, it remains that increased metabolic activity (SUVmax) of primary tumors has been repetitively shown a negative effect on the prognosis of NSCLC (Xu et al., 2008; Agarwal et al., 2010; Paesmans et al., 2010; Zhang et al., 2011). Worsening of prognosis in NSCLC with a high SUVmax may be partly due to an increase of local extension, and nodal or distant organ metastasis as demonstrated in our study. However, optimal threshold of SUVmax and the type of threshold used for SUVmax are varying from one study to another. At the same time, there are a few contrary data on the prognostic role of increased FDG uptake of primary tumor (Vesselle et al., 2007; Ikushima et al., 2010).

There were some limitations in our study. Firstly, the sample size is relatively small; in particular there were only 27 cases without any metastasis on $^{18}$F-FDG PET-CT. Further studies with larger patient groups are needed to assess the relationship between primary tumor SUVmax and local extension, nodal and distant organ metastases in patients with NSCLC. Secondly, the local extension, nodal and distant organ metastases were determined according to PET-CT not the gold standard of pathological findings, so the results should be verified with further follow-up. Additionally, we concluded that SUVmax of primary tumor was correlated with tumor size; however, we did not recommend a potentially accurate method to correct the SUV for partial volume effects. The partial volume effects can significantly lower the SUV when the tumor size is less than 2 to 3 cm (Vesselle et al., 2007), so a systemic research should be carried out for the relationship between the corrected SUV and tumor size.

In conclusion, we have shown that the patients of NSCLC with high SUVmax present significantly more frequent local extension, and nodal or distant organ metastases than patients with low SUVmax. Patients with NSCLC having high SUVmax might be candidate for more aggressive or more individualized treatment to achieve better disease control. Furthermore, they may need a close follow-up because of their higher extensional and metastatic potential.

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The author(s) declare that they have no competing interests.

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