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Relationship between primary tumor FDG uptake and extensional or metastatic potential in patients with small cell lung cancer

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Abstract

Objective: To explore the maximum standardized uptake value (SUVmax) of primary tumors, as well as the relationship between SUVmax with tumor size, with tumor stage or with lymph nodal metastasis in small cell lung cancer (SCLC) patients who underwent 18F-fluorodeoxyglucose positron emission tomography–computed tomography (18F-FDG PET-CT) for staging before initial treatment.

Methods: Thirty-two patients with SCLC who underwent 18F-FDG PET-CT scans before treatment were included in this study. Primary tumor SUVmax was calculated, and clinical stage, presence of local extension, as well as nodal and distant organ metastases were recorded. The patients were divided into low and high SUVmax groups by using the median SUVmax. The low SUVmax group consisted of 16 patients with SUVmax<8.41, while the high SUVmax group consisted of 16 patients with SUVmax≥8.41. The data from the two groups were compared for statistical differences.This study was approved by the Institute Research Medical Ethics Committee of Bach Mai hospital.

Results: Thirty-two cases were included for analysis. The SUVmax ranged from 2.36 to 20.40 (mean 9.99±4.84). In the low SUV group, 3 patients had local extension, 1 had nodal metastasis, and 13 haddistant organ metastasis. In the high SUV group, 5 patients had local extension, 12 had nodal metastasis, and 11 had distant organ metastases. There were nosignificant differences in local extension (P>0.05), distant organmetastasis (P>0.05), or in nodal metastasis rate (P>0.05) between the low SUV versus high SUV groups. In addition, there was a moderate correlation between SUVmax and tumor size (r=0.504, P=0.003), SUVmax and tumor stage(r=0.432, P=0.014), but not SUVmax and node stage (r=-0.195, P=0.284) or SUVmaxand overall stage (r=-0.317, P=0.077).

Conclusion: SUVmax was associated with tumor size, but not with distant metastases or lymph node involvement in patients with small cell lung cancer. Thus, SUVmax determined by 18F-FDGPET-CT is not predictive of the presence of metastases.

Keywords: 18F-FDG PET-CT, SUVmax, tumor stage, lymph nodal, small cell lung cancer (SCLC)

Introduction

Lung cancer is among the most common tumor types, representing 13% of newly diagnosed cancers worldwide. Both the absolute and relative frequencies of lung cancer have risen dramatically. Unfortunately, it remains by far the leading cause of cancer-related deaths, accounting for 18% of the total number of deaths [1]. Small cell lung cancer (SCLC), accounting for 10% of clinical lung cancer cases, is an aggressive malignancy strongly associated with smoking. It displays a distinct natural history characterized by a high growth fraction, rapid doubling time and early establishment of widespread metastatic lesions [2].

In patients with SCLC, it is important to determine whether the cancer is at alimited stage (LS) or extensive stage (ES).

LS cancers, which are potentially curable, are treated with chemotherapy and radiation, with surgical resection reserved for selected patients with stage I disease. ES cancers are incurable; systemic chemotherapy is used to improve quality of life and prolong survival [3].

Until 2011, the National Comprehensive Cancer Network (NCCN) recommended a (99m)Tc-MDP bone scan as part of the initial evaluation of all newly diagnosed SCLC patients. However, in 2012, the NCCN began recommending 18F-fluorodeoxyglucose positron emission tomography–computed tomography (18F-FDG PET-CT) in lieu of bone scan in its initial workup algorithm. PET has emerged in the last decade as an important tool in the staging and delineation of disease

for conformal radiotherapy planning of non-SCLC. In 2009, Medicare approved the use of PET for the initial staging of SCLC. It is believed that PET may more accurately detect patients with ES disease than CT-staging alone. This stage migration allows physicians to withhold potentially toxic radiation therapy from poorer prognosis ES patients who would not benefit from it. With better ability to identify patients who will likely respond to treatment, stage-specific survival will improve [4].

Indeed, 18F-FDG PET-CT provides morphological and metabolic data of malignancy,and has become an important non-invasive tool for staging as well as assessment of the primary tumor and distant metastases in lung cancer. FDG uptake in the primary tumor is measured as the maximum standardized uptake value (SUVmax) by PET. SUVmax indicates the disease activity or the aggressiveness of tumor, can be easily obtained, and is the most widely used parameter for the analysis of 18F-FDG PET images in clinical practice. Metastasis occurs primarily by dissemination not only through the lymphatic and blood vessels but via local extension in SCLC. However, to date, few studies have evaluated the relationship between the primary tumor SUVmax and extensional or metastatic potentialin patients with SCLC.

In this study, we aim to explore the SUVmax of the primary tumor, as well as the relationship of SUVmax with tumor size, with tumor stage, and withand nodal or distant organ metastasisin SCLC patients who underwent 18F-FDG PET-CT for staging before initial treatment.

Materials and Methods
Clinical data
We retrospectively analyzed the 18F-FDG PET-CT findings of 32 newly diagnosed SCLC patients with amean age of 61 years (range: 38-81 years), between December 2016 and October 2018. Patients were enrolled by convenient sampling method. There were 29 (90.6%) males, and 3 (9.4%) females.All patients were defined by histological or cytological evidence. The patients were referred to Bach Mai Nuclear Medicine and Oncology Center for initial staging with PET-CT scan before treatment. Histological diagnosis of the tumors was based on the criteria of the 2015 World Health Organization [5], and the tumor-node-metastasis (TNM) stage was determined according to the 8th Lung Cancer TNM classification by the International Association for the Study of Lung Cancer.This study was approved by the Institute Research Medical Ethics Committee of Bach Mai hospital.

FDG PET-CT imaging
18F-FDG PET-CT scans were performed with awhole-body PET-CT scanner. All patients had been fasting for at least 6 hours before PET imaging, and serum glucose levels were measured to ensure that the results were180 mg/dl. All patients had a glucose level below 180 mg/dl and were injected intravenously with 0.15-0.20 mCi/kg (7-12mCi) FDG. At 45-

60 min after the injection, data were acquired from the vertex to the upper thigh. Immediately after CT, a PET scan (PET-CT Biograph True Point, Siemens, Germany) was performed for approximately 25 min, with 7 to 8 bed positions and 3 min/position. PET images were reconstructed iteratively with CT data for attenuation correction, using an inline integrated Siemens Esoft Workstation system (Germany). CT-integrated PET fusion images in transaxial, sagittal, and coronal planes were evaluated visually, and the SUVmax of lesions was obtained from transaxial images.

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 SCLC 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 recordedfrom the workstation. Both radiologists who conducted the measurements together were blinded to the clinical details.

Statistical analysis
Statistical analysis was done using SPSS 22.0 (Chicago, Illinois, USA). The mean of the measurement data was expressed as mean±standard deviation (mean±S.D.). The differences of tumor SUVmax in independent groups were compared using independent 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 SUVmaxusing Spearman's correlation. P-values less than 0.05 were considered significant.

Results
The SUVmax ranged from 2.36 to 20.40 (mean 9.99±4.84). The median SUVmax was 8.41, the low SUVmax group ranged from 2.36 to 8.32 (mean of 6.19±1.93), and the high SUVmax group ranged from 8.49 to 20.40 (mean of 13.80±3.72). The clinical characteristics of patients in the low and high groups are shown in **Table 1**.

Local extension, lymph node, and distant organ metastasis in the low and high group are shown in **Table 2**. Local extension (including primary tumor invasion to the main bronchus, visceral pleura, chest wall, mediastinum, and recurrent laryngeal nerve) were seen in 3 patients (18.8%) in the low SUVmax group and 5 patients (31.2%) in the high SUVmax group (P>0.05 between the groups). Lymph node and distant organ metastases were not different in the low SUVmax (68.8%, 11/16; 81.2%, 13/16) compared to those of the high SUVmax group (75.0%, 12/16; 68.8%, 11/16) (P >0.05 between the groups).

In addition, Spearman's rank correlation showed a significant association of SUVmax ofprimary tumor with tumor size, tumor stage, nodal stage, and overall stage of the patients (**Table 3**).
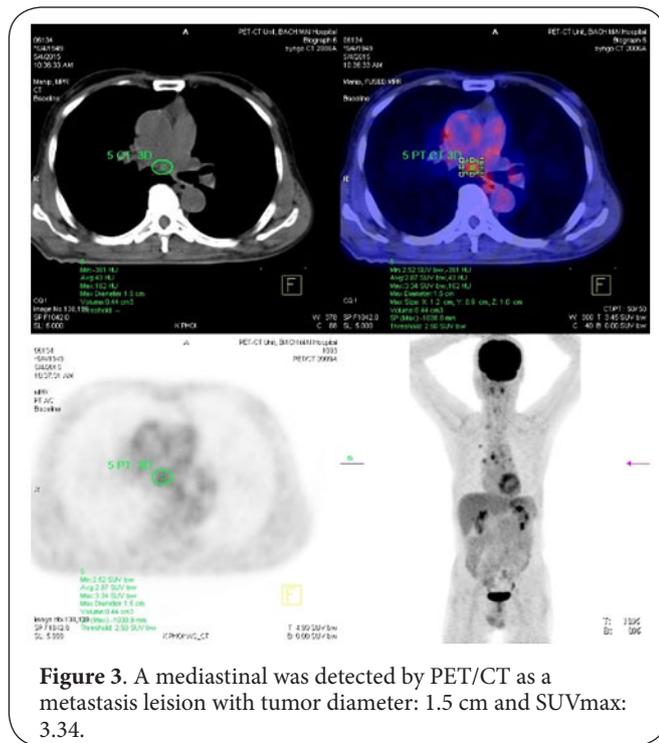
Table 1. Clinical Characteristics of Patients (n=32).

Characteristics	No. of patients and percentage	
	Low SUVmax group (SUVmax <8.41), (n=16)	High SUVmax group (SUVmax ≥8.41), (n=16)
Age (38–81 years)		
< 59 years	8 (50%)	4 (25%)
≥ 59 years	8 (50%)	12 (75%)
Sex		
Male	13 (81.2%)	16 (100%)
Female	3 (18.8%)	0 (0%)
Tumor location		
Left upper lobe	6 (37.5%)	7 (43.75%)
Left lower lobe	1 (6.25%)	0 (0%)
Right upper lobe	5 (31.25%)	5 (31.25%)
Right middle lobe	1 (6.25%)	2 (12.5%)
Right lower lobe	3 (18.75%)	2 (12.5%)
TNM stage		
I	0 (0%)	1 (6.2%)
II	1 (6.2%)	1 (6.2%)
III	3 (18.8%)	5 (31.2%)
IV	12 (75.0%)	9 (56.2%)

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

	Low SUVmax group (SUVmax <8.41)	High SUVmax group (SUVmax ≥8.41)	P-value
Local extension (%)	3 (18.8%)	5 (31.2%)	>0.05
Lymph node metastasis (%)	11 (68.8%)	12 (75.0%)	>0.05
Distant organ metastasis (%)	13 (81.2%)	11 (68.8%)	>0.05

Table 3. Correlation of SUVmax and Tumor Size or Tumor Stage.

	Correlation coefficient	P-value
Tumor diameter	0.504	0.003
Tumor stage	0.432	0.014
Node stage	-0.195	0.284
Overall stage	-0.317	0.077

Figures 1-4 are the PET-CT images of patient with SCLC at stage IV, according to the TNM classification.

Discussion

Although CT or magnetic resonance imaging (MRI) provides precise anatomical and morphological information, the role of FDG-PET-CT has increased for diagnosis and staging of lung cancer [6]. Recently, FDG uptake has been reported to be a prognostic factor in patients with lung cancer [6-8]. Patz et al. [9] demonstrated that patients with positive FDG-PET-CT results, after treatment for lung cancer, had a significantly worse

Figure 1. The primary tumor located at upper right lobe with tumor diameter was 11.1 cm and SUVmax was 11.40.

Figure 2. A leision located at upper left lobe was detected on PET/CT as lung metastasis with tumor diameter: 0.6 cm and SUVmax: 2.55.

prognosis than patients with negative results. Therefore, we examined whether SUVmax correlates with tumor size, with lymph node, or with distant metastases in patients with SCLC.

We studied the value of SUVmax in patients diagnosed with SCLC. Median SUVmax value of the primary tumor of the total study population was 8.41 (range 2.36 to 20.40) and

Figure 3. A mediastinal was detected by PET/CT as a metastasis leision with tumor diameter: 1.5 cm and SUVmax: 3.34.
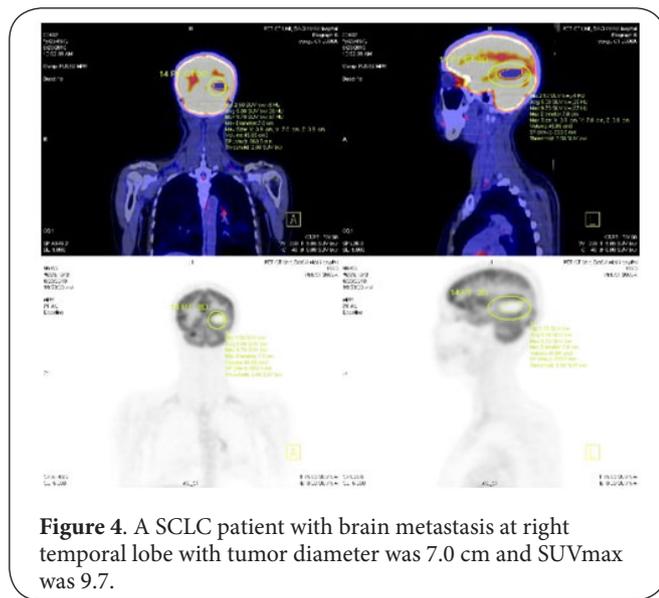

Figure 4. A SCLC patient with brain metastasis at right temporal lobe with tumor diameter was 7.0 cm and SUVmax was 9.7.

the mean was 9.99±4.84). Tumor size, but not lymph node or distant metastases, was found to be related to the tumor SUVmax in our study. Our data was different from the observations of van der Leest el al. [10] which studied in 75 chemo-naive patientsand showed that median SUVmax value of the primary tumor of the total study population was 11.3 (range 1.18–25.99). And, SUVmax of the primary tumor was significantly higher in the patients with stage IV disease compared to stage I–III disease. This can be mainly explained

that our population sample size was smaller and most of our patients at stage IV according to TNM classification.

The association between the SUVmax and tumor size could be useful in choosing the appropriate treatment such as chemotherapy or surgery. And, this result could help future researches with SUVmaxas a predict factor in patients with SCLC if there is any relationship between primary tumor SUVmax and survival time.

FDG PET-CT is an important adjunct examination in the evaluation of SCLC, combining functional information (FDG PET) with anatomic information (CT). FDG PET-CT is invaluable in clinical staging, restaging, guiding therapy, and suggesting prognosis. SCLC is readily identified by FDG PET because of the high metabolic activity of this cancer type. Some studies have reported improved staging accuracy with FDG PET compared with CT alone, and that FDG PET-CT is more accurate than FDG PET alone [10,16-18]. The use of FDG PET in ES-SCLC in 19% of patients and to down staging from ES-SCLC to LS-SCLC in 8% of patients. Although FDG PET is inferior to CT or MR imaging for the detection of brain metastases, it is more sensitive and specific than conventional imaging for detecting metastatic disease [19]. 18F-FDG PET-CT has been increasingly used for staging, treatment response assessment, and therapy planning in lung cancer since it was introduced into clinical practice in 1998 [20].

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 it is least affected by partial volume effects [21]. SUVmax is also defined as a unique noninvasive method for studying biochemical and metastatic changes in cancer tissues [22]. The relationships between SUVmax of primary tumor with local extension, with lymph node, and with distant organ metastasis were investigated.

Our results showed that the increases of lymph nodes and of distant organ metastasis do not correlatewith increasing primary tumor SUVmax in SCLC patients. In addition, the results showed that local extension of the primary tumor (such as the main bronchus, visceral pleura, chest wall, or mediastinum) were not different in the high SUVmax group when compared to the low SUVmax group; these results had not yet been reported elsewhere.

SUVmax has been correlated with tumor proliferation rate, tumor grade, and expression of glucose transporters, which are biomarkers in various types of malignant tumors. Metastasis is the major cause of death due to several malignancies, including SCLC, and it occurs primarily by dissemination through the lymphatic and blood vessels. Nambu et al. (2009) have reported that the likelihood of lymph node metastasis increases with the increase of SUVmax of the primary tumor in patients with NSCLC [23]. Our results are different from their observations. In their study, they also noted that when the SUVmax of the primary tumor was greater than 12, the probability of lymph

node metastasis was high, reaching 70%, irrespective of the degree of FDG accumulation into the lymph node stations. Thus, such results in NSCLC allow to more sensitively predict the presence of lymph node metastases, including microscopic ones that cannot be detected by direct evaluation of the lymph node stations. This difference between SCLC and NSCLC can be explained by the high growth fraction, rapid doubling time and early establishment of widespread metastatic lesions in SCLC than those in NSCLC. Most SCLC patients in our study were diagnosed at the stage IV according to TNM classification. Therefore, the SUVmax is not varied significantly by lymph node stagesand metastasis stages.

In patients with NSCLC, Zhu et al. [24] have shown that the average SUVmax was significantly lower in patients without any metastasis than in those with lymph node and/or distant organ metastasis. They suggested that SUVmax may, in part, reflect the potential of metastasis of the primary tumor in NSCLC. 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 utility of PET in the initial staging of patients with SCLC has been evaluated in several studies comparing pre-treatment 18F-FDGPET to conventional staging procedures [14,17,25-28] (**Table 4**). Study designs varied with regards to the extent of conventional staging, the use of PET alone or PET-CT, and the method used to define PET positivity. In addition, some studies required biopsies of all FDG-avid lesions that would alter stage, whereas others used clinical follow-up to confirm PET findings. Unfortunately, several studies did not validate PET findings and stage alterations by either method.

SCLC is a highly metabolic malignancy, leading to a sensitivity of 100% for PET detection of primary tumors. Overall, cumulative staging concordance was 84% between PET and conventional imaging, with better concordance noted in prospective (89%, range 83–100%) rather than retrospective (80%, range 67–100%) studies [29]. Of the 204 patients with LS-SCLC by conventional imaging, 19% were up-staged to ES by PET, with similar findings in the prospective (17%, range 0–33%) and retrospective (20%, range 0–54%) studies. Of the 199 patients with ES-SCLC by conventional imaging, 11% were down-staged to LS by PET, with a much lower percentage of down-staged patients noted in the prospective (5%, range 0–11%) than retrospective (18%, range 0–40%) studies. For metastatic sites, PET was superior to standard imaging in terms of both sensitivity and specificity. However, PET was inferior to MRI or CT for the detection of brain metastases [29].

There were some limitations in our study. Firstly, the sample size was relatively small. Particularly, there were only 3 cases without any metastasis (by 18F-FDG PET-CT). Further studies with larger patient groups are needed toassess the relationship between primary tumor SUVmaxand local extension, nodal or distant organ metastases inpatients with SCLC. Secondly, local extension, as well as nodaland distant organ metastases, were determined accordingto PET-CT, not the gold standard of pathological findings. Thus, the results need to be verified as afollow-up. Additionally, we conclude that the SUVmax of the primary tumor is correlated with tumor size. However, we do not recommend a potentially accurate method to correct the SUV for partial volume effects; these effectscan significantly lower the SUV when the tumor size isless than 2 to 3 cm [30]. Thus, further research should be carried out to explore the relationship ofcorrected SUV with tumor size.

Conclusion

In conclusion, we have shown that SUVmax is associated with tumor size, but not with distant metastases or lymph node involvement in patients with SCLC. This type of lung cancer is hight malignancy and rapid metastasis with most patients is presented at stage IV. Thus, SUVmax determined by FDG-PET-CT is not predictive of the presence of metastases at

Table 4. PET for initial staging of SCLC.

Trial	N	Stage concordance (%)	LS		ES	
			N	Up-staged (LS→ES) (%)	N	Down-staged (ES→LS) (%)
Prospective						
Chin [18]	18	38	9	22	9	11
Bradley [12]	24	88	24	88	0	-
Brink [19]	120	88	51	20	69	4
Kut [13]	18	100	6	0	12	0
Fisher [15]	29	83	9	33	20	5
Retrospective						
Haubner [25]	7	100	6	0	1	0
Schumacher [27]	26	73	13	54	13	0
Shen [28]	25	92	10	10	15	7
Blum [17]	15	67	15	33	0	-
Azad [14]	46	74	26	15	20	40

advanced stage. Larger prospective and randomized analyses may potentially reveal more significant relationships.

List of abbreviation
FDG: fluorodeoxyglucose
SUVmax: maximum standardized uptake value
SCLC: small cell lung cancer
18F-FDG PET-CT: 18F-fluorodeoxyglucose positron emission tomography–computed tomography
LS:limited stage
ES: extensive stage
TNM: tumor-node-metastasis

Competing interests
The author declares that he has no competing interests.

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