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Original Research Article

Can positron emission tomography - computed tomography imaging predict of metastases in patients with small cell lung cancer

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ABSTRACT

Background: Small-cell lung cancer (SCLC) accounts for 15%-20% of all lung cancer cases. Positron emission tomography - computed tomography (PET/CT) has become increasingly used as an initial staging tool in patients with SCLC. We aimed to explore the relationships between primary tumor 18F-FDG uptake measured as the maximum standardized uptake value (SUV max) and clinical stage at PET/CT for small cell lung cancer patients (SCLC).
Methods: Patients with SCLC who underwent 18F-FDG PET/CT scans before the treatment were included in the study at Bach Mai hospital of Vietnam, from November 2014 to May 2018. The primary tumor and secondary lesion SUVmax was calculated; the tumor size was measured; the TNM status was determined mainly by FDG PET/CT imaging according to The 8th Edition of the TNM Classification for Lung Cancer were recorded. An evaluation was made of the linear relationship between tumor size, T stage, N stage, and M stages of the patients and their SUVmax using Spearman's correlation.
Results: Total 37 cases (34 men and 3 women; age range 38 - 81 years, median 64 years) were analyzed. The average of primary tumor size and SUVmax were 5.95±2.77 cm and 10.21±4.75, respectively. The SUVmax of primary tumor is significantly greater than that of nodal and distant organ metastasis (10.21±4.75 vs 8.20±4.35 and 6.44±3.17, $p<0.01$). There was a moderate correlation between SUVmax and tumor size ($r =0.596$, $p<0.001$), tumor stage ($r = 0.502$, $p<0.01$) but not significant with nodal stage ($r =-0.218$, $p=0.194$), metastasis stage ($r = -0.055$, $p=0.747$), and overall stage ($r=-0.060$, $p=0.725$).
Conclusions: SUVmax was significantly correlated with tumor size, but not with distant metastases or lymph node involvement. Therefore, SUVmax on positron emission tomography is not predictive of the presence of metastases in patients with SCLC.

Keywords: Maximum standardized uptake value, Positron emission tomography - computed tomography, Small-cell lung cancer

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide. Small cell lung cancer (SCLC) represented approximately 10-15% of all lung cancers.[1,2] Smoking is the main risk factor for SCLC, approximately 95% of these patients were smokers.[3] SCLC is characterized by the low degree of differentiation, shorter doubling time and high sensitivity to chemotherapy and radiotherapy.

Each year, 13% of all newly diagnosed lung cancer patients are diagnosed with SCLC.[4] Approximately 39% of patients with SCLC are diagnosed with limited-stage disease treated with chemotherapy and definitive radiation therapy. Staging information is essential because of the high propensity for metastatic disease in SCLC, and the identification of metastases can spare patients from the toxicity associated with thoracic radiotherapy. Furthermore, in those patients who do

receive radiotherapy, knowing the exact extent of intrathoracic disease may permit more accurate treatment volume delineation.

Positron emission tomography (PET) has emerged in the last decade as an important tool in the staging and delineation of disease for conformal radiotherapy planning of non-small cell lung cancer (NSCLC). In 2009, Medicare approved the use of PET for the initial staging of SCLC.[5] It is believed that PET may more accurately detect patients with extensive-stage disease than computed tomography (CT) staging alone.[6] According to the International Association of the Study of Lung Cancer, TNM staging is recommended, based on tumor, node, and metastasis staging, it is useful for the patients who are candidate for surgery.

The aim of the present study was to investigate the relationship between FDG uptake (maximum standardized uptake value) and clinical stage for small cell lung cancer.

METHODS

The present study was approved by the Institutional Review Board of Bach Mai Hospital (Ha Noi, Vietnam). A retrospective review of the medical records of patients with SCLC who had undergone baseline 18F-FDG-PET/CT prior to initial therapy was conducted. Written informed consent was obtained from each patient prior to each PET/CT scan. A total of 37 consecutive patients (62.0±9.4 years) who were pathologically diagnosed with SCLC at Bach Mai Hospital between November 2015 and October 2018 were included in the present study.

Inclusion criteria

- All patients had a pre-therapy baseline PET/CT scan
- Patients had no history or concurrent diagnosis of another type of cancer.

Patients were excluded for the following reasons: primary lesion smaller than 1 cm (to ensure feasibility of partial volume correction), histology could not be confirmed or was confirmed as other than SCLC, type I diabetes, prior history of lung cancer or other prior cancer within the previous 5 years, previous therapy or surgical staging for SCLC before PET.

FGD/PET imaging

All patients underwent diagnostic and/or staging FDG-PET-CT prior to biopsy or therapy. Patients were asked to fast at least 6 h before the FDG-PET-CT scan. 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 about 25 min, with seven to eight 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. Computerized tomography integrated positron emission tomography fusion images in transaxial, sagittal, and coronal planes were evaluated visually, and the SUVmax of lesions was obtained from transaxial images.

CT determination of tumor size

Tumor size was determined by averaging all 3 diameters of the primary tumor, measured on the mediastinal windows of the chest CT, using printed films. CT scans were obtained either at our institution or by the referring physician.

Statistical evaluation

Nonparametric, rank-based statistical methods were chosen because none of our measurements (maxSUV, tumor size, TNM stage) could be assumed to have a normal distribution. Comparisons were therefore performed using a Kruskal–Wallis (KW) nonparametric test. Correlations between pairs of variables (i.e., maxSUV versus tumor size) were evaluated using the Spearman rank (SR) correlation test. All analyses were conducted using SPSS version 22.0.

RESULTS

In total, 37 patients fulfilled the inclusion criteria with the mean of age was 62.0±9.4 years (range 38-81 years) and the male/female ratio was 11.3/1. The characteristics and SUVmax of the patients are summarized in Table 1.

Table 1: Characteristics and SUVmax of the SCLC cases n (%) SUV (mean±SD).

	n (%)	SUV (mean±SD)	p value
Age			
<61	14 (37.8)	9.22±4.03	0.287
≥61	23 (62.2)	10.82±5.12	
Sex			
Male	34 (91.9)	10.28±4.81	0.824
Female	3 (8.1)	9.40±4.76	
Tumor size			
≤3 cm	6 (16.2)	5.47±3.57	0.006
>3cm ≤5 cm	9 (24.3)	8.53±4.49	
>5 cm	22 (59.5)	12.19±4.02	
TNM overall stage			
I, II	3 (8.1)	8.95±8.08	0.446
III	11 (29.7)	11.75±4.19	
IV	23 (62.2)	9.64±4.60	

There was not difference of SUVmax between age group of <61 and ≥61 age (p=0.287). The primary tumor

SUVmax of male patients was not different to those in female group (10.28±4.81 vs 10.82±5.12, p=0.824). When the cases were divided into three groups based on tumor size (group 1, <3 cm; group 2, >3 cm and <5 cm; and group 3, >5 cm), tumor SUVmax was differ significantly between groups 1, 2 and 3 (p = 0.006). Considering all cases, tumor SUVmax was not significantly correlated with age, gender or TNM overall stage (p=0.446).

The average of primary tumor size and SUVmax were 5.95±2.77 cm and 10.21±4.75, respectively. The SUVmax of primary tumor is significantly greater than that of nodal and distant organ metastasis (10.21±4.75 vs 8.20±4.35 and 6.44±3.17, p<0.01) showed in the Figure 1.

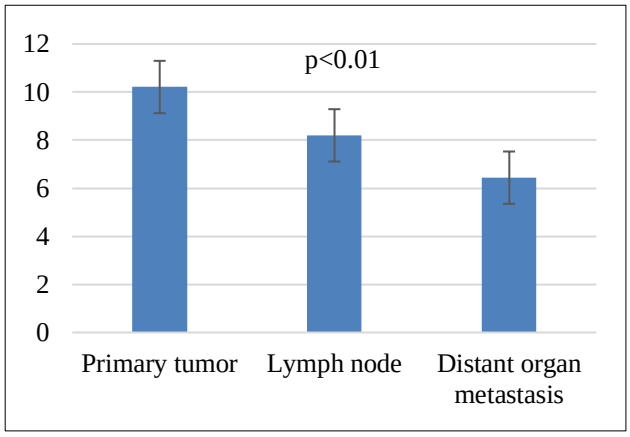

Figure 1: Comparison of SUVmax between primary tumors, lymph nodes and distant organ metastases.

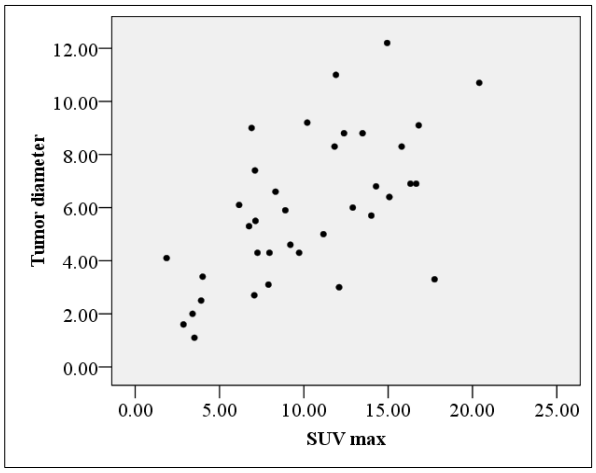

Figure 2: Correlation between SUVmax and tumor size (r =0.596, p<0.001).

There was a moderate correlation between SUVmax and tumor size (r =0.596, p<0.001), tumor stage (r = 0.502, p<0.01) but not significant with nodal stage (r =-0.218, p=0.194), metastasis stage (r = -0.055, p=0.747), and overall stage (r=-0.060, p=0.725) in the figure 2, figure 3, figure 4, figure 5 and figure 6, respectively.

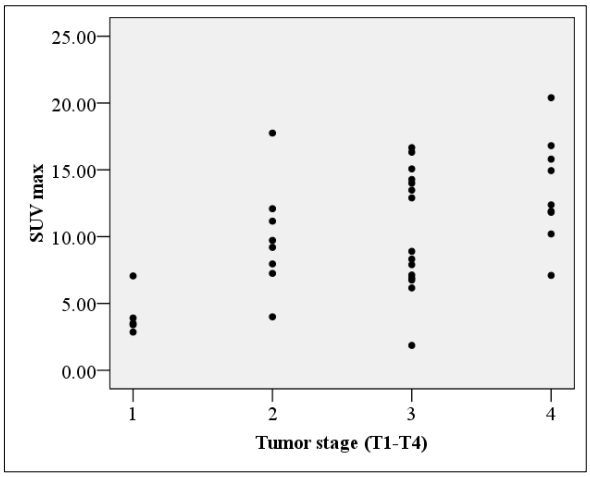

Figure 3: Correlation between SUVmax and tumor stage (r = 0.502, p<0.01).

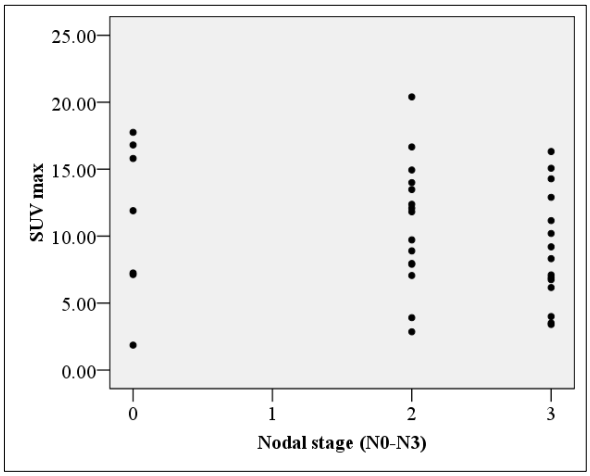

Figure 4: Correlation between SUVmax and nodal stage (r =-0.218, p=0.194).

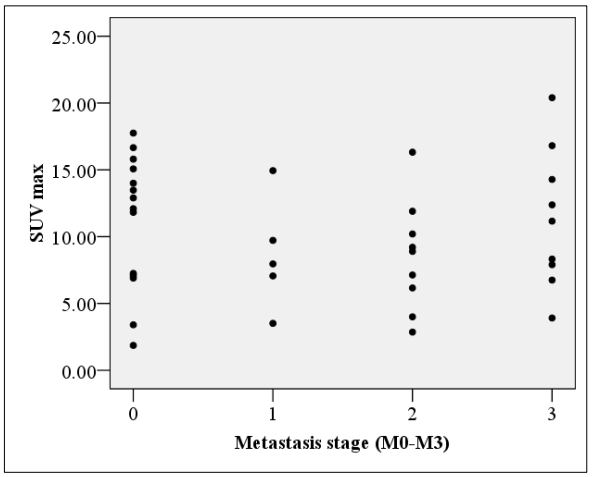

Figure 5: Correlation between SUVmax and metastasis stage (r = -0.055, p=0.747).

One case of SCLC had the primary tumor located at the left lung. The tumor had the diameter of 3.9cm and

SUVmax of 8.91 (Figure 7). PET/CT found the mediastinal nodal metastase with diameter of 3.8 cm and SUVmax of 7.78 (Figure 8); as well as spinal bone metastase with diameter of 4.2 (Figure 9).

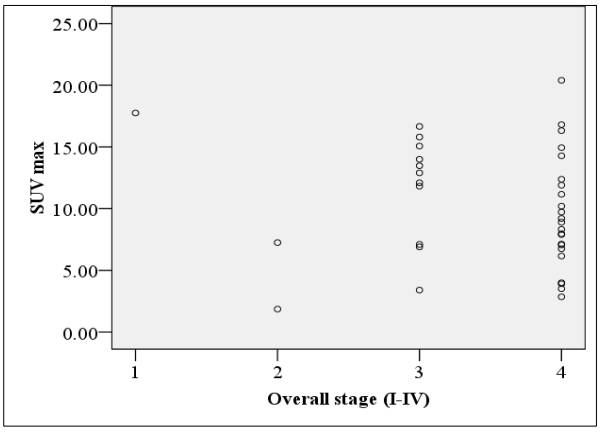

Figure 6: Correlation between SUVmax and overall stage (r=-0.060, p=0.725).

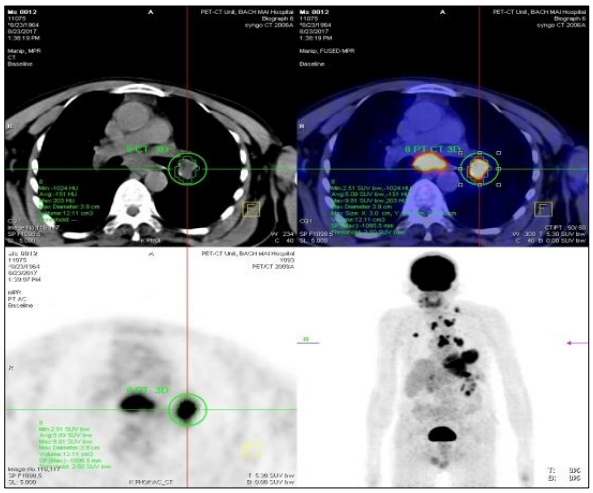

Figure 7: The primary tumor.

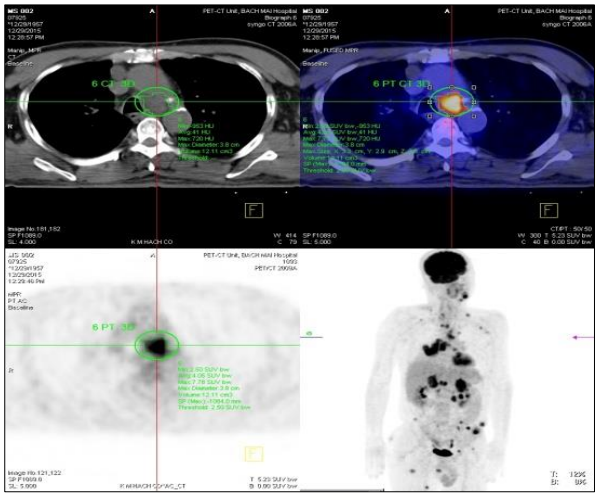

Figure 8: Mediastinal nodal metastase.

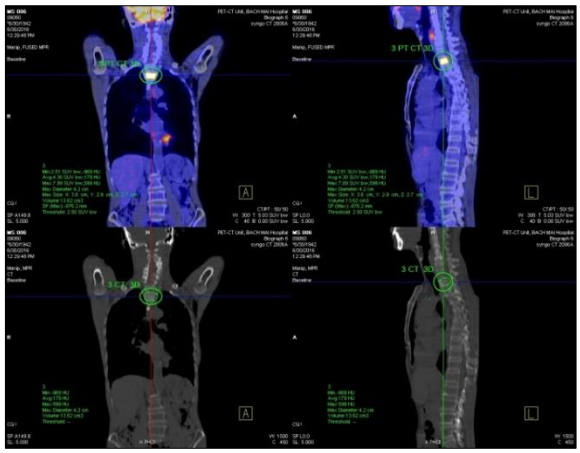

Figure 9: Spinal bone metastase.

DISCUSSION

Although CT or magnetic resonance imaging provides precise anatomical and morphological information, the role of FDG-PET-CT has increased for diagnosis and staging of lung cancer. Recently, FDG uptake has been reported to be a prognostic factor in patients with lung cancer.[3] Patz et al demonstrated that patients with positive FDG-PET-CT results in treated lung cancer had a significantly worse prognosis than patients with negative results.[7] Therefore, we examined whether SUVmax correlates with tumor size, TNM stage in patients with SCLC. Tumor size, tumor stage but not lymph node or distant metastases, was related to the tumor SUVmax. Doom et al also reported a strong significant association between tumor size and SUVmax in patients with NSCLC.[8] Another study in patients with stage I NSCLC showed a significant association between the primary tumor, SUVmax and tumor size, with tumors <3 cm having a significantly lower SUV than tumors >3 cm.[6] Many studies regarding the correlation between SUVmax and other features such as histology, clinics in patients with NSCLC but no reports in SCLC has been found so far.

Fluorodeoxyglucose-PET-CT is already an indispensable modality for evaluating lymph node and distant metastases. Many reports have suggested that FDG-PET-CT is superior to CT in the accuracy of N- staging for lung cancer. Therefore, FDG-PET-CT is now regarded as the most accurate imaging modality for N- staging of lung cancer. However, a significant number of false-negative and false-positive findings of lung cancer, including N-staging, on FDG-PET-CT have been reported. Nambu et al demonstrated that the likelihood of lymph node metastasis increased with an increase in SUVmax of the primary tumor; for primary lung cancer with a SUVmax greater than 12, the probability of lymph node metastasis was high, reaching 70%, irrespective of the degree of FDG accumulation in the lymph node stations.[9] They concluded that this finding would allow a more sensitive prediction of the presence of lymph node

metastases, including the microscopic ones that cannot be detected by direct evaluation of lymph node stations. Consistent with these results, Higashi et al documented in a multicenter study that the incidence of lymphatic vessel invasion and lymph node metastasis in NSCLC were associated with 18 F-FDG uptake, concluding that 18 F-FDG uptake by a primary tumor is a strong predictor of lymphatic vessel invasion and lymph node metastasis.[10] In the present study, although tumor SUVmax was higher in patients with lymph node metastasis than in those without, the difference did not reach statistical significance.

It was also observed that the frequency of lymph node metastasis was higher in adenocarcinomas (80.2%) than in squamous cell carcinomas (71.4%), suggesting that pathological subtype may be a significant factor associated with lymph node metastasis. In contrast, a previous study showed no difference in the frequency of lymph node metastasis between the two pathological subtypes. Based on univariate analysis, Jeong et al concluded that metastasis detected by PET imaging, which can affect staging by aiding in the discovery of metastasis to contralateral lymph nodes or distant organs, was an insignificant factor, and that metastatic findings on PET had weak discriminative power.[11] According to Cerfolio et al, FDG-PET-CT does not replace the need for tissue biopsies for staging N1 or N2 lymph nodes, or metastatic lesions, as false positives and false negatives were observed in all stations in their study.[12]

However, FDG-PET-CT resulted in better patient selection before pulmonary resection. FDG-PET can also help in targeting areas for biopsy and identifying unsuspected N2 and Ml disease. In the present study, tumor SUVmax was not significantly correlated with distant metastases. This may be attributable to the finding of increased 18 F-FDG uptake by subclinical inflammatory lesions as well as by malignant tumors.

CONCLUSION

SUVmax was associated with tumor size, tumor stage but not with distant metastases or lymph node involvement. Thus, SUVmax determined by FDG-PET-CT is not predictive of the presence of metastases in patients with SCLC. Larger prospective and randomized analyses may potentially reveal more significant relationships.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Bach Mai Hospital

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