

Comparison of Primary Tumor SUVmax Between Small Cell Lung Cancer and Non-Small Cell Lung Cancer



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Abstract

Objective: The objective of the present study is to compare of primary tumor SUVmax between small cell lung cancer and non-small cell lung cancer.

Methods: Patients with lung cancer who underwent 18F-FDG PET-CT scans before the treatment were included in the study at Bach Mai hospital of Vietnam, from November 2015 to May 2018. The primary tumor SUVmax was calculated; the tumor size was measured; the T-N-M status was determined mainly by FDG PET-CT imaging according to the 8th Edition of the TNM Classification for Lung Cancer were recorded. A comparison of primary tumor SUVmax between SCLC and NSCLC was made using Mann Whitney U test.

Results: 519 cases (40 SCLC and 319 NSCLC) were analyzed. The primary tumor SUVmax of NSCLC is significantly greater than that of SCLC (10.96 ± 5.42 vs 8.09 ± 3.99 , respectively, $p=0.001$). ROC area under the curve of primary tumor SUVmax for NSCLC involvement was 0.795 (95% CI: 0.750-0.836), $p<0.0001$. An optimal cut-off value was identified as 8.39 by ROC curve, the sensitivity and specificity were 94% and 60%, respectively. There was a moderate correlation between SUVmax and tumor size ($r = 0.542$, $p<0.001$) in NSCLC but not significant in SCLC ($r = 0.279$, $p=0.081$). There was a moderate between SUVmax and TNM overall stage in NSCLC ($r=0.513$, $p=0.01$) but not significant in SCLC ($r = 0.145$, $p=0.173$).

Conclusion: PET-CT could contribute to the differential diagnosis of NSCLC with SCLC with high sensitivity but low specificity. In addition, SCLC is more aggressive than NSCLC, presenting with a rapid doubling time and higher propensity for widespread metastatic disease.

Keywords: Maximum standard uptake value (Suvmax); Primary tumor; Small cell lung cancer (SCLC); Non-small cell lung cancer (NSCLC)

Abbreviations: Suvmax: Maximum Standard Uptake Value; NSCLC: Non Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer; PET-CT: Positron Emission Tomography-Computed Tomography; FDG: Fluorodeoxyglucose

Introduction

Lung cancer is the leading cause of death due to cancer around the world, with 1.59 million deaths per year [1]. In spite of the progress achieved in treating these patients, survival after 5 years is still poor, with approximately 15% - 16% [2-4]. Tobacco is the main risk factor for lung cancer, increasing the likelihood of suffering this type of cancer 10 times more than a person who has not been exposed to it. Other conditions associated to a greater risk of lung cancer are idiopathic pulmonary fibrosis and exposcarcinogens such as asbestos [5,6]. Non-small cell lung cancer (NSCLC), which is the predominant histology (seen in 85-90% of all cases of lung cancer), encompasses three subtypes: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. The remaining 10-15% of cases are small cell lung cancer (SCLC) [7].

The assessment of patients with suspected lung cancer has routinely included morphological imaging evaluation, with either chest X-rays or CT of the thorax. More recently, the emergence of combined PET/CT imaging has greatly aided the investigation of lung cancer by allowing even better delineation of areas with increased tracer uptake. This modality has helped radiologists avoid the technical difficulties that arose from the independent combination of PET and CT examinations, which resulted in substantial artifacts. In addition, PET/CT has been shown to be an accurate tool for the work-up of solitary pulmonary nodules (SPNs) and for lung cancer staging-by improving the detection of metastatic disease, guiding therapy, and allowing clinical outcomes to be predicted [8,9].

¹⁸F-FDG PET has been reported to be useful in characterizing solitary pulmonary nodules [10], improving lung cancer staging [11], guiding therapy, monitoring treatment response [12] and predicting outcome [13]. The role of ¹⁸F-fluorothymidine (¹⁸F-FLT), an indirect marker of cells proliferation, has also been suggested for NSCLC and SCLC patients evaluation. For patients with lung carcinoma, the accurate determination of tumor type significantly influences treatment decision making. In general, SCLC is much more responsive to chemotherapy and consequently this comprises the mainstay of treatment. This is in contrast to NSCLC, which includes adenocarcinomas, squamous cell carcinomas, and large cell undifferentiated carcinomas of the lung. Therefore, this study sought to compare of primary tumor SUVmax between small cell lung cancer and non-small cell lung cancer.

Methods

Clinical Data

We retrospectively analyzed the ¹⁸F-FDG PET-CT findings of 359 newly diagnosed lung cancer patients (40 SCLC and 319 NSCLC), between December 2015 and October 2018. There were 257 (71.6%) males, and 102 (28.4%) females. All patients were defined by histological or cytological evidences. 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 [14] and the tumor-node metastasis (TNM) stage was determined according to the 8th lung cancer TNM classification of International Association for the Study of Lung Cancer.

FDG PET-CT Imaging

¹⁸F-FDG PET-CT scans were performed with a wholebody 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 were 180 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 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.

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 recorded from 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 (SCLC and NSCLC) were compared using Mann Whitney U 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. Receiver operating characteristics (ROC) curve analysis was used to explore sensitivity and specificity for SUVmax and evaluated the optimal cutoff values for SUVmax in distinguish the primary tumor between NSCLC and SCLC. All tests of significance were two-sided; P<0.05 was considered significant.

Results

Table 1: Characteristics of the SCLC and NSCLC.

Characteristics		SCLC (n=40)	NSCLC (n=319)	P value
Age	< 61	15 (37.5%)	156 (48.9%)	0.173
	≥ 61	25 (62.5%)	163 (51.1%)	
Sex	Male	36 (90.0%)	211 (69.3%)	0.006
	Female	4 (10.0%)	98 (30.7%)	
Tumor size	≤ 3 cm	5 (12.5%)	88 (27.6%)	0.006
	> 3 ≤ 5 cm	10 (25.0%)	114 (35.7%)	
	> 5 cm	25 (62.5%)	117 (36.7%)	
Tumor location	Left upper lobe	17 (42.5%)	100 (31.3%)	0.052
	Left lower lobe	3 (7.5%)	47 (14.7%)	
	Right upper lobe	4 (10.0%)	71 (22.3%)	
	Right middle lobe	12 (30.0%)	53 (16.6%)	
	Right lower lobe	4 (10.0%)	48 (15.0%)	

TNM overall stage	I	2 (5%)	19 (6.0%)	0.935
	II	3 (7.5%)	29 (9.1%)	
	III	14 (35%)	97 (30.4%)	
	IV	21 (52.5%)	174 (54.5%)	

The characteristics and SUVmax of the 40 SCLC cases and 319 NSCLC cases are summarized in Table 1. Male were more frequent than female in both SCLC and NSCLC. The ratio male / female were much more in SCLC compare to that in NSCLC (9/1 vs 2.2/1, respectively, $p=0.006$). Tumor size >5cm in diameter were more frequent in SCLC (62.5%, 25/40) than that of NSCLC (36.7%, 117/319), ($p = 0.006$). The tumor is likely to locate more

frequently in upper lobe than others. The other characteristics including age, sex, tumor location, TNM overall stage between two groups were not different. The average of primary tumor size of SCLC is significantly greater than that of NSCLC (5.9 ± 2.5 cm vs 4.9 ± 2.4 cm, $p=0.002$), while average of primary tumor SUVmax of SCLC is significantly smaller than that of NSCLC (8.09 ± 3.99 vs 10.96 ± 5.42 cm, $p=0.001$), showed in the Figures 1 & 2 (Table 1).

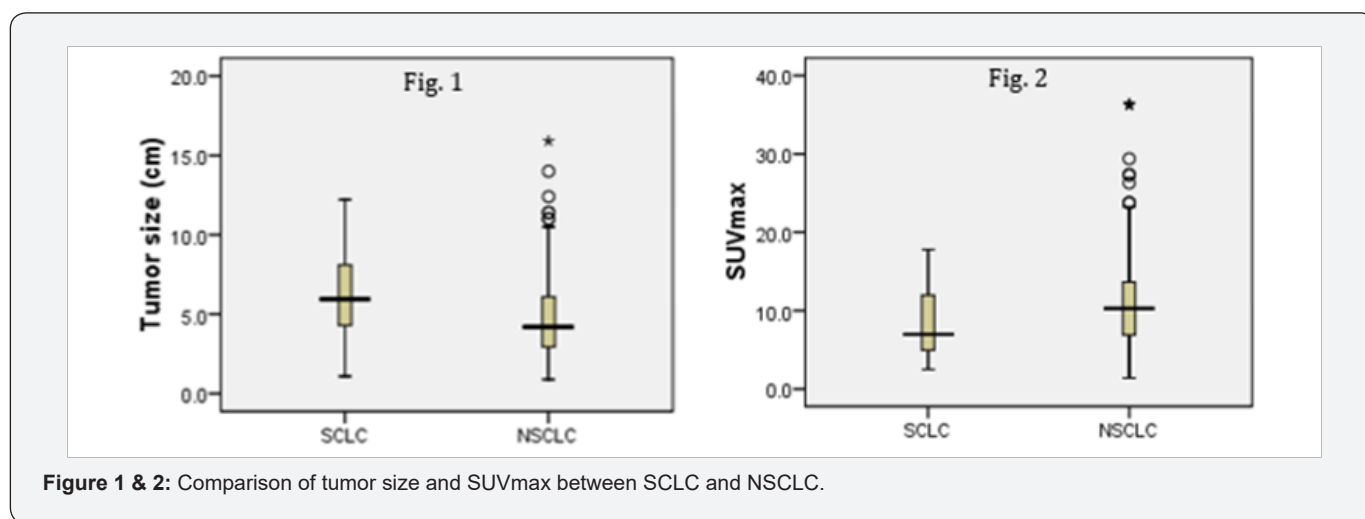


Figure 1 & 2: Comparison of tumor size and SUVmax between SCLC and NSCLC.

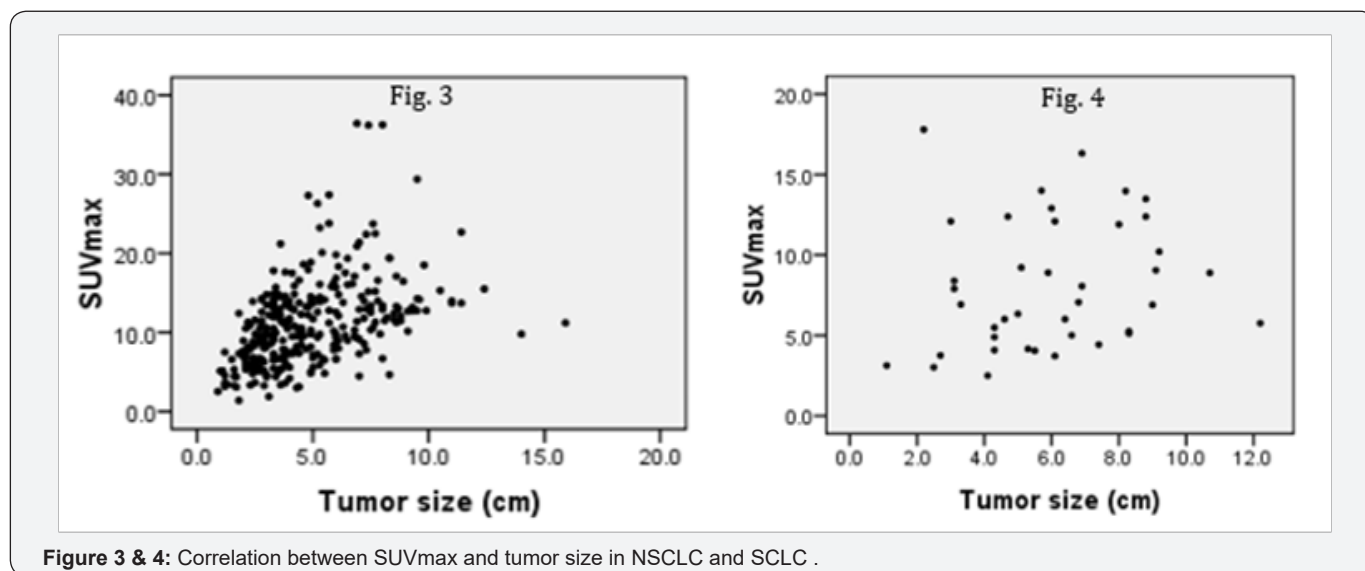


Figure 3 & 4: Correlation between SUVmax and tumor size in NSCLC and SCLC .

There was a moderate correlation between SUVmax and tumor size ($r = 0.542$, $p < 0.001$) in NSCLC but not significant in SCLC ($r = 0.279$, $p = 0.081$) showed in Figures 3 & 4. There was a moderate between SUVmax and TNM overall stage in NSCLC ($r = 0.513$, $p = 0.01$) but not significant in SCLC ($r = 0.145$, $p = 0.173$). ROC area under the curve of primary tumor SUVmax for NSCLC

involvement was 0.795 (95% CI: 0.750-0.836), $p < 0.0001$. An optimal cut-off value was identified as 8.39 by ROC curve, the sensitivity and specificity were 94.7% and 60%, respectively (Figure 5). Figures 6 & 7 shows the PET-CT images of patients with SCLC and NSCLC.

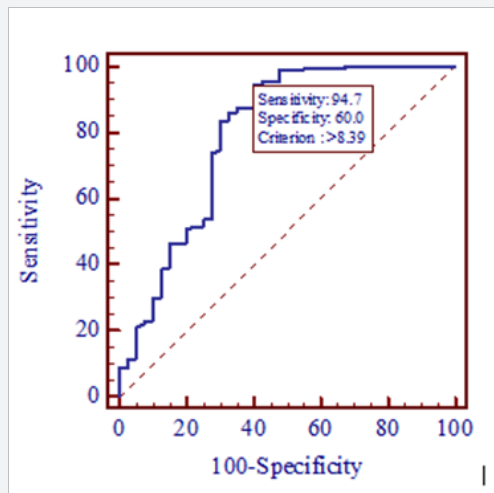


Figure 5: ROC curve of SUVmax to distinguish primary tumor of NSCLC from SCLC. Overall accuracy was good, with area under ROC curve of 0.795 (95% CI: 0.750–0.836), $p < 0.0001$.

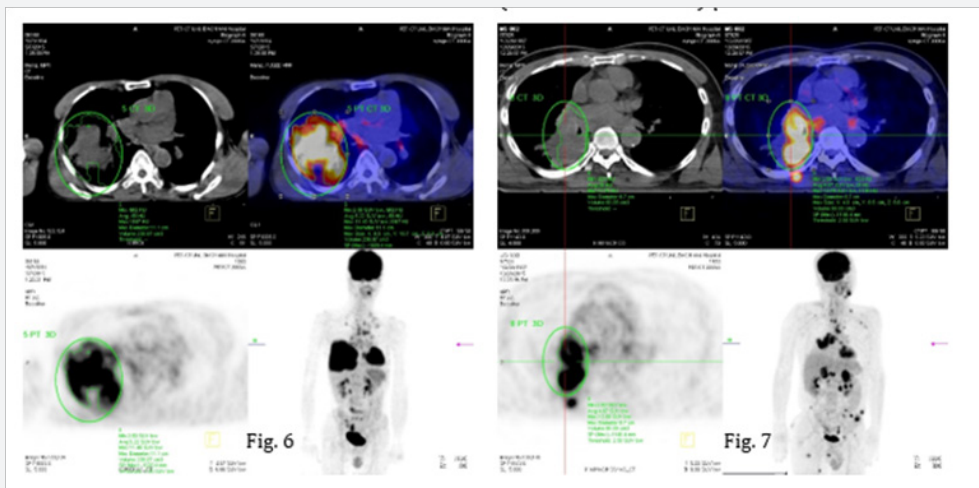


Figure 6 & 7: PET-CT images of primary tumor. In case of SCLC (fig. 6), the tumor diameter is 11 cm and SUVmax is 11.4. The other is a case of NSCLC (fig. 7) with the tumor diameter and SUVmax of 8.7 cm and 13, respectively.

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 [15]. Patz et al. [16] demonstrated that patients with positive FDG-PET-CT results in treated lung cancer had a significantly worse prognosis than patients with negative results. Therefore, we examined whether SUVmax correlates with tumor size, TNM stage in patients with lung cancer.

For patients with lung carcinoma, the accurate determination of tumor type significantly influences treatment decision making. In general, SCLC is much more responsive to chemotherapy and

consequently this comprises the mainstay of treatment. This is in contrast to NSCLC, which includes adenocarcinomas, squamous cell carcinomas, and large cell undifferentiated carcinomas of the lung.

Clinically, SCLC is more aggressive than non-small cell lung cancer (NSCLC), presenting with a rapid doubling time and higher propensity for widespread metastatic disease. Overall prognosis is severe: in fact, despite initial chemosensitivity, most patients with SCLC relapse and die from recurrent disease [17,18]. The impact of PET on stage classification of newly diagnosed SCLC has been investigated by several authors that reported how PET allowed a modification of stage and clinical management in 10-33% of cases. Fischer et al. reported that PET/CT could improve accuracy of SCLC staging with a higher sensitivity

than conventional imaging (93% vs. 79%, respectively) and equal specificity (100%). In their population PET/CT findings determined a change of stage in 5 of 29 patients (17%) [19].

In a population of 120 SCLC patients studied for staging by PET and conventional imaging, PET up-staged 10 patients and down-staged 3 patients [20]. Overall PET data resulted in a change of stage in 12% of patients. In a recent study Azad et al. found that PET altered stage classification in 12 of 46 (26%) patients when compared with conventional imaging. In particular, among the 26 patients with limited disease on conventional imaging, 4/26 (15%) were accurately upstaged to extended disease after PET while among the 20 patients with extended disease on conventional imaging, 8/20 (40%) were downstaged to limited disease [21].

Only in one study PET did not alter stage classification in SCLC patients: infect Kut et al. [22], in their population, found that PET scan findings agreed with conventional imaging in the majority of cases [22]. In patients with NSCLC, Özgül et al. [23] examined whether SUVmax correlates with tumor size, lymph node and distant metastases in patients with NSCLC. Tumor size, but not lymph node or distant metastases, was related to the tumor SUVmax [23]. Doom et al. [24] also reported a strong significant association between tumor size and SUVmax in patients with NSCLC. 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 [25]. In addition, a retrospective analysis of 85 patients with solid pulmonary lesions found a positive correlation between the size of a malignant tumor and SUVmax [26]. A multivariate analysis demonstrated that the combination of high SUV and large lesion size identified a subgroup of patients with the worst prognosis and a median survival rate of less than 6 months [27].

Conclusion

The primary tumor SUVmax of NSCLC is significantly greater than that of SCLC. PET-CT could contribute to the differential diagnosis of NSCLC with SCLC with high sensitivity but low specificity. In addition, SCLC is more aggressive than NSCLC, presenting with a rapid doubling time and higher propensity for widespread metastatic disease.

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