**Original Article**

**Running Title:** Prognostic Factors for Small Cell Lung Cancer

# PET/CT as a Prognostic Factor for Small Cell Lung Cancer

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## Abstract

**Background:** Small cell lung cancer (SCLC) is known to be an aggressive cancer with poor prognosis. Prognostic factors are essential for the prediction of treatment outcomes and survival. The present study aimed to evaluate the prognostic value of $^{18}$F-fluorodeoxyglucose-positron emission tomography/computed tomography ($^{18}$F-FDG-PET/CT) in patients with SCLC.

**Method:** In this retrospective study, the medical records of 41 patients with SCLC were reviewed; these patients underwent pre-treatment FDG-PET/CT and presented to our institution from January 2012 to December 2017. PET/CT parameters, clinical factors, treatment, and follow-up data were collected and correlated to the overall survival (OS).

**Results:** The median age of the patients was 61 years, only five of whom (12.2%) were females. Additionally, 29 patients (70.7%) were smokers, 9 (22%) were ex-smokers, and 3 (7.3%) were none-smokers. Among our subjects, 13 (31.7%) had limited stage disease while 28 (68.3%) presented with extensive stage disease. The median pre-treatment maximum standardized uptake value (SUVmax) for the primary tumor was 14.54. The median OS was 18.1 months. Based on univariate analysis, SUVmax, stage, age, and sex were significantly associated with OS. However, smoking status, tumor side, and lobe location had no significant impact on OS. Furthermore, according to multivariate analysis, SUVmax, stage, and age were independent prognostic factors for OS.

**Conclusion:** SUVmax, age, and tumor stage were found to be significant prognostic factors for OS in patients with SCLC.

***Keywords*:** Lung neoplasms, Positron emission tomography/computed tomography, Prognosis, Survival

## Introduction

Small cell lung cancer (SCLC) is an aggressive malignancy with a high proliferation index and a strong predilection for early dissemination.[1] SCLC accounts for about 15% of all newly-diagnosed lung cancer patients.[1,2] Unlike other tumors, SCLC is clinically staged into only two stages, namely limited disease (LD) and extensive disease (ED), according to tumor extent. LD stage is defined as a disease confined to the ipsilateral hemithorax, which can be encompassed by a single radiation port. Meanwhile, ED is considered to be a disease extending beyond the ipsilateral hemithorax or associated with malignant pleural effusion.[3]

Despite extensive basic and clinical research and major improvements in the anti-cancer treatment modalities over the past decades, the prognosis of SCLC still remains inadequate with frequent local recurrence and/or distant metastasis; that mentioned, the median overall survival (OS) does not exceed two years with the available treatment.[4]

A better understanding of prognostic factors allows for a better interpretation of the results of the clinical trials, better tailoring of treatment policy, and more accurate prediction of treatment outcomes and survival. Hence, different clinical parameters, including clinical stage, performance status, gender, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), serum sodium, and serum albumin levels, have been proposed as prognostic markers for survival in patients with SCLC.[4-6]

In SCLC, $^{18}$F-fluorodeoxyglucose-positron emission tomography/computed tomography ($^{18}$F-FDG-PET/CT) has been proven to be an essential imaging tool in the diagnosis, staging, and early evaluation of treatment response. However, the prognostic value of $^{18}$F-FDG-PET/CT in SCLC is still controversial with only scarce data.[7-11] Therefore, this study assessed the prognostic value of $^{18}$F-FDG-PET/CT together with other clinical factors in patients with SCLC.

## Material and Methods

### *Patients*

In this retrospective study, the medical records of 41 patients with pathologically proven SCLC were reviewed; the subjects underwent pre-treatment $^{18}$F-FDG-PET/CT scan and presented to the Department of Oncology and Nuclear Medicine, Alexandria University Hospital, from January 2012 to December 2017. Among our subjects, 13 (31.7%) had limited stage disease while 28 (68.3%) presented with extensive stage disease. $^{18}$F-FDG-PET/CT parameters, clinical factors, such as age, sex, stage, tumor side, tumor site, and smoking status, the treatment, and follow-up data were collected and correlated to OS. Our institutional research Ethics Committee approved of the present work, which is registered under the code 159/29/29/8/2013.

### *$^{18}$F-FDG-PET/CT imaging*

Whole body PET/CT scans were performed using the GE discovery VCT (GE Healthcare, Waukesha, WI, US 53188) scanner. All the patients had a fasting period of at least 6 hours, whose blood glucose levels were < 180 mg/dl prior to the scanning. The patients were scanned one hour after intravenous injection of 300 MBq of $^{18}$F-FDG in a supine position with their arms extended above their heads in a cranio-caudal direction from the base of the skull to the upper thighs in quiet respiration. Initially, multislice CT scans (120 kV, 100 mAs, 5

mm slice thickness) were obtained for attenuation correction and anatomical localization without IV or oral contrast enhancement, followed by the PET scan. Uncorrected emission images and CT-based attenuation-corrected images were reconstructed. Using the standard formula, the standardized uptake values (SUVs) of $^{18}$ F-FDG were calculated for the region of interest (ROI) from the PET attenuation-corrected emission images. The maximum standardized uptake value (SUVmax) within the primary lung tumor was determined for each patient.

***Statistical analysis***

Statistical analyses herein were performed using SPSS (v. 22) software (SPSS Inc., Chicago, IL, USA). OS was considered as the primary endpoint and calculated from the date of diagnosis to the date of death or date of the last follow-up. The patients were dichotomized into two groups according to the median of SUVmax ($\leq$ 14.54 vs. > 14.54) and median age ($\leq$ 61years vs. > 61years), sex (male vs. female), tumor stage (LD vs. ED), and tumor side (left hemithorax vs. right hemithorax). Smoking status was categorized into non-smokers, smokers, and ex-smokers, and tumor lobe location into upper, middle, and lower. OS curves were estimated using the Kaplan–Meier product-limit method and the difference among the groups was tested with two-sided log-rank test. A multiple Cox's proportional hazard regression model was carried out using enter selection (with the first subset as the indicator) for parameters that were significant in the univariate analysis; the estimated hazard ratio (HR) with 95% confidence interval (CI) was further calculated. A $P \leq 0.05$ was considered as statistically significant.

## Results

***Patients and tumor characteristics***

As shown in Table 1, the median age of the patients was 61 years (range: 44-74 years). Only five patients (12.2%) were female. Regarding smoking status, 29 patients (70.7%) were smokers, nine (22%) were ex-smokers, and three (7.3%) were none-smokers. Approximately two thirds of the subjects (61%) presented with primary tumor located in the right hemithorax and 16 patients (39%) had left hemithoracic lesions. The tumor was located in the upper lobe in 19 (46.3%), the middle lobe in 10 (24.4%), and the lower lobe in 12 patients (29.3%). The median pre-treatment SUVmax for the primary tumor was 14.54 (range 3.58 - 27.75).

***Treatment***

Out of the 13 patients with LD, 8 (19.5%) received concurrent chemoradiotherapy, 2 (4.9%) received only radiotherapy, and 3 (7.3%) were treated through chemotherapy alone; the patients showing complete or partial response underwent prophylactic cranial irradiation consisting of 25Gy in 10 fractions. All the 28 patients (68.3%) with ED received palliative chemotherapy Cisplatin plus Etoposide (Cisplatin 30 mg/m$^2$ on days 1–3 and Etoposide 100 mg/m$^2$ on days 1–3) or Carboplatin plus Etoposide (Carboplatin AUC 5 or 300 mg/m$^2$ on day 1 and Etoposide 100 mg/m$^2$ on days 1–3) (Table 1).

***OS***

The median follow-up time was 22 months (range: 1.5-48 months), and the median OS was 18.1 months. Based on univariate analysis (Table 2), the patients with high SUVmax had significantly shorter ($P$ = 0.000) OS compared to those with low SUVmax (Figure 1a). The subjects presenting with ED also showed significantly shorter ($P$ = 0.003) OS in comparison to those with LD (Figure 1b). The median OS was significantly unfavorable ($P$ = 0.025) in the patients

older than 61 years (Figure 1c). Our female subjects had significantly better ($P$ = 0.005) OS than their male counterparts (Figure 1d). However, according to univariate analysis, smoking status ($P$ = 0.774), tumor side ($P$ = 0.631), and lobe location of the tumor ($P$ = 0.433) had no significant impact on OS. In multivariate analysis (Table 2), SUVmax ($P$ = 0.005), tumor stage ($P$ = 0.037), and age ($P$ = 0.046) were significant prognostic factors for OS. The patients with high SUVmax, presenting with ED, or older than 61 years had a significantly poor OS.

## Discussion

Several studies have addressed the prognostic role of $^{18}$F-FDG-PET/CT in SCLC patients with contradictory results.[12-19] Although SUV is a widely utilized semiquantitative index for assessing the metabolic activity of tumor tissues, there is no universal method for the measurement or calculation of $^{18}$F-FDG uptake. In the current study, SUVmax was selected as a metabolic parameter for tumor $^{18}$F-FDG uptake as it is the most easily reproducible and commonly reported metric. In addition, we hypothesized that the identified SUVmax value would represent a surrogate marker for real SCLC metabolic activity.

The present study demonstrated that SCLC patients with high SUVmax values in the primary tumor in pretreatment $^{18}$F-FDG-PET/CT had poor prognosis. Consistent with our results, Pandit et al. retrospectively evaluated the prognostic value of $^{18}$F-FDG-PET imaging in 46 SCLC patients and found a significant negative correlation ($P$ = 0.0021) between SUVmax and survival, concluding that a high SUVmax was significantly associated with poor survival.[12] In addition, Aktan et al. assessed the prognostic value of pre-treatment $^{18}$F-FDG-PET parameters on clinical outcomes in 46 patients with limited stage SCLC treated with concurrent chemoradiotherapy. They reported that the median OS was significantly shorter ($P$ = 0.027) in patients with high pretreatment SUVmax compared to those with low SUVmax.[13]

The underlying mechanisms through which a high $^{18}$F-FDG uptake (meaning a high SUVmax on the $^{18}$F-FDG-PET test) is associated with poor prognosis are yet to be determined. However, this might be explained by the presence of hypoxic areas within the tumor, which is usually resistant to anti-cancer treatments, especially radiotherapy, and leads to unfavorable outcomes.[14] It is well known that tumors with abundant hypoxic areas often have worse prognoses. In addition, hypoxic conditions usually stimulate more and more glycolysis in tumor cells than in normoxic conditions.[15] Moreover; tumor hypoxia activates hypoxia inducible factor-1α (HIF-1α) pathway, thereby increasing the number of glucose transporters on the cell membranes of malignant cells, leading to enhanced $^{18}$F-FDG uptake by tumor cells.[16]

However, some studies have reported contrasting results. Zhu et al. retrospectively evaluated the prognostic significance of $^{18}$F-FDG-PET/CT in 98 patients with SCLC and found that SUVmax did not show any correlation with OS.[17] Park et al. also assessed the prognostic value of PET parameters in 202 patients with SCLC and reported no significant difference in their survival according to SUVmax.[18] In this study, however, PET parameters of all intrathoracic (lung, pleura, and mediastinum) malignant hypermetabolic lesions were measured, where the highest SUVmax was adopted as a prognostic variable and not only for primary tumor, such as the ones in our study. In another

study by Oh et al., high SUVmax (≥ 10.4) was not a significant factor for poor prognosis in 106 patients with SCLC.[19] Nevertheless, unlike the present study, SUVmax was measured in all malignant lesions. The measurement of PET parameters in all malignant hypermetabolic lesions may be time-consuming and not available in routine clinical practice. Therefore, it was advantageous for our study to evaluate the PET parameter from primary lung lesion only using SUVmax which is relatively easy to measure.

We found on multivariate analysis that tumor stage and age were independent prognostic factors, which is in accordance with various previous reports.[20–24]

This study encountered certain limitations, such as its retrospective nature, small number of patients, and the fact that not all clinical prognostic factors were tested. In addition, SUVmax is represented by a single-pixel value of $^{18}$F-FDG uptake and does not reveal the heterogeneous nature of the tumor. However, SUVmax is convenient to measure, commonly used, and highly reproducible to reflect the metabolic activity of malignant tissues obtained via PET imaging.

## Conclusion

In conclusion, SUVmax of a primary tumor is an important prognostic factor for OS in patients with SCLC, in addition to age and tumor stage. The SUVmax, together with age and stage, should be taken into consideration when determining the treatment policy for patients with SCLC.

## Conflict of Interest

None declared.

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Table 1. Patients and tumor characteristics

| | n | % |
|---|---|---|
| **Age (median)** | 61 range: 44-74y | |
| **SUVmax (median)** | 14.54 range: 3.58 - 27.75 | |
| **Sex** | | |
| Male | 36 | 87.8 |
| Female | 5 | 12.2 |
| **Smoking** | | |
| None-smoker | 3 | 7.3 |
| Smoker | 29 | 70.7 |
| Ex-smoker | 9 | 22.0 |
| **Stage** | | |
| LD | 13 | 31.7 |
| ED | 28 | 68.3 |
| **Hemithorax** | | |
| Left | 16 | 39.0 |
| Right | 25 | 61.0 |
| **Lobe** | | |
| Upper | 19 | 46.3 |
| Middle | 10 | 24.4 |
| Lower | 12 | 29.3 |
| **Therapy of LD** | | |
| Concurrent CRT | 8 | 19.5 |
| Chemotherapy | 3 | 7.3 |
| Radiotherapy | 2 | 4.9 |
| **Therapy of ED** | | |
| Chemotherapy | 28 | 68.3 |

SUVmax: Maximum standardized uptake value; LD: Limited disease; ED: Extensive disease; CRT: Concurrent chemoradiotherapy

Table 2. Univariate and multivariate analyses of the overall survival

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Median (months) | SE | *P* value | HR | (95% CI) | *P* value |
| SUVmax | | | 0.000 | 6.64 | (1.76 - 25.11) | 0.005 |
| ≤ 14.54 | 28.9 | 7.3 | | | | |
| > 14.54 | 11.8 | 0.3 | | | | |
| Stage | | | 0.003 | 3.86 | (1.09 - 13.74) | 0.037 |
| LD | 28.9 | 4.2 | | | | |
| ED | 11.9 | 1.5 | | | | |
| Sex | | | 0.005 | 0.00 | (0.00 - 2.45) | 0.952 |
| Male | 16.9 | 2.6 | | | | |
| Female | - | - | | | | |
| Age | | | 0.025 | 2.85 | (1.02 - 8.00) | 0.046 |
| ≤ 61years | 25.5 | 6.7 | | | | |
| > 61years | 11.8 | 0.7 | | | | |
| Hemithorax | | | 0.631 | | | |
| Left | 17.9 | 1.8 | | | | |
| Right | 18.7 | 4.3 | | | | |
| Lobe | | | 0.433 | | | |
| Upper | 17.9 | 8.8 | | | | |
| Middle | 18.7 | 7.0 | | | | |
| Lower | 18.1 | 4.9 | | | | |
| Smoking | | | 0.774 | | | |
| None-smoker | 11.1 | - | | | | |
| Smoker | 16.9 | 7.3 | | | | |
| Ex-smoker | 18.1 | 0.3 | | | | |

SUVmax: Maximum standardized uptake value; LD: Limited disease; ED: Extensive disease; SE: Standard error, HR: Hazard ratio; CI: Confidence interval

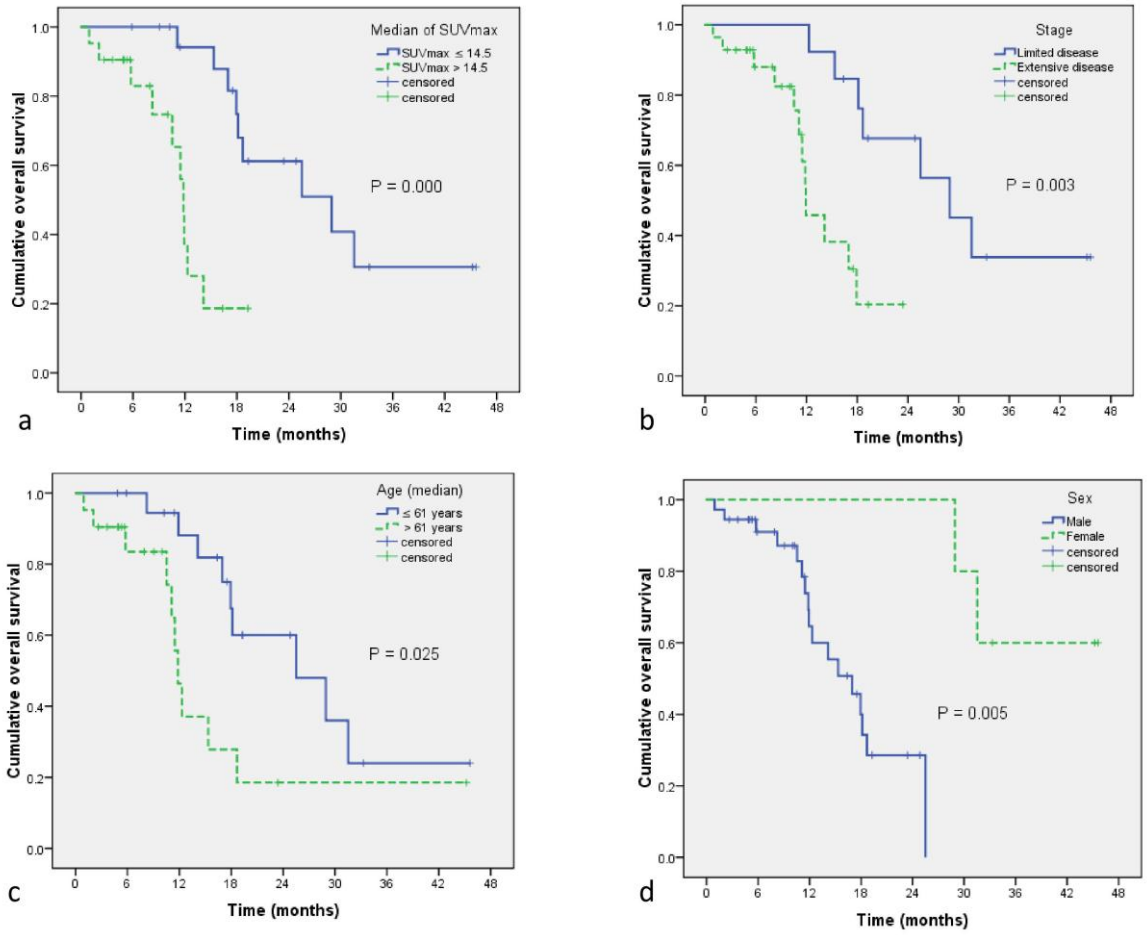


Figure 1. This figure shows the overall survival rates of 41 patients with small cell lung cancer according to SUVmax (a), stage (b), age (c), and sex (d).