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^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography for predicting prognosis of small cell lung cancer patients

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► ***Original article***

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ABSTRACT

***Background*:** The purpose of this study is to evaluate the accuracy of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/Computed Tomography (PET/CT) in predicting tumor prognosis in patients with Small Cell Lung Cancer (SCLC). ***Materials and Methods*:** From July 2015 to March 2019, all 30 SCLC patients who had analyzable PET/CTs and adequate clinical data were evaluated. Medical records were retrospectively reviewed, including age, gender, stage, performance status according to the Eastern Cooperative Oncology Group (ECOG), metabolic parameters on PET and treatment programs. Factors potentially affecting tumor prognosis were examined by models of univariate and multivariate Cox proportional hazards regression. ***Results*:** The median age of the cohort was 58 years (range: 39-93). A median follow-up period of 12 months was observed. Multivariate Cox proportional hazards regression demonstrated that the overall survival (OS) ($p = 0.03$) and progression-free survival (PFS) ($p = 0.014$) were related only to the metabolic tumor volume (MTV). The optimal cutoff threshold was 98 mm^3, and the receiver operating characteristic (ROC) curve had an area under it of 0.75. In comparison to the high-MTV group, the low-MTV group had statistically substantially prolonged OS ($p = 0.004$) and PFS ($p < 0.001$). ***Conclusion*:** The MTV of ^{18}F-FDG PET/CT is a major independent prognostic factor in SCLC patients and has significant implications for OS and PSF.

INTRODUCTION

Lung cancer ranks among the most prevalent cancers globally, of which approximately 15% are small cell lung cancer (SCLC) [1]. Despite its susceptibility to initial radiation and chemotherapy, it is distinguished by a high growth percentage, a rapid time to double, and the early emergence of widespread metastases, which cause repeatedly relapsing and a bleak prognosis [2].

As a result of the Veterans Administration Lung Cancer Study Group's work, a two-stage classification system has been developed that categorizes SCLC patients into two categories: limited disease (LD) and extensive disease (ED). A single radiation port can treat LD, which affects just the ipsilateral hemithorax [3]. In recent times, it has been suggested to stage SCLC using the tumor, node, and metastasis (TNM) system. Traditionally, preventive cranial irradiation is used after combination chemoradiotherapy for patients with stage I–III cancer who respond to treatment. Palliative chemotherapy is the backbone of treatment for stage IV cancer [4, 5].

From the 1970s through the 1990s, as chemotherapy was added to the treatment of SCLC, the median survival rate and five-year survival rates significantly improved. However, survival rates for both localized and advanced SCLC appear to have peaked [6]. Additionally, despite the improvements in SCLC outcome, the majority of patients still have disease progression after finishing therapy, with 40% showing an isolated local recurrence as their initial site of progression [7].

Additionally, the therapy has a significant degree of toxicity, with up to 30% of patients developing grade three or worse esophagitis [8]. In order to choose the patients most likely to benefit from therapy, accurate prognostic indicators are thus required. By doing so, it may be possible to prevent unsuccessful treatments and the resulting side effects and expenses.

Over the last decade, an essential technique for staging NSCLC is ^{18}F-fluorodeoxyglucose positron emission tomography/Computed Tomography (^{18}F-FDG PET/CT). The technique is increasingly used for planning conformal radiotherapy in the early stages of treatment response evaluation, recurrence diagnosis, and disease characterization. ^{18}F-FDG tumor uptake on PET in NSCLC and other malignant tumors, as determined by the standardized uptake value (SUV), has recently become a significant predictive indicator [9-12]. The amount of tumor

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tissues with higher ^{18}F-FDG uptake is known as metabolic tumor volume (MTV), and it has also been demonstrated to be a significant independent prognostic factor in esophageal carcinoma and head and neck cancer [13-15]. However, metabolic parameters have been largely unexplored to predict survival and clinical utility in SCLC. An assessment of the prognostic significance of ^{18}F-FDG PET/CT has now been conducted in a group of patients with SCLC that has been more specifically defined. We seek to clarify whether various PET metrics predict survival and disease control. We also take into account other clinically significant variables when evaluating the predictive usefulness of PET measures.

MATERIALS AND METHODS

Patients

The institutional review board granted permission for this retrospective investigation while waiving informed consent. All SCLC patients (n=57) who received a baseline whole-body FDG-PET scan were assessed between July 2015 and March 2019. Medical records were retrospectively conducted, including age, including age, gender, stage, performance status according to the Eastern Cooperative Oncology Group (ECOG), metabolic parameters on PET, and treatment programs. Out of 57 patients, 30 had analyzable PET/CTs and adequate clinical data. The pursuing eligibility criteria were applied: i) diagnosis of primary SCLC based on histology or cytology; ii) underwent a complete body ^{18}F-FDG PET/CT scan before beginning therapy; and iii) medical records with adequate clinical data.

^{18}F-FDG PET/CT imaging

A full-ring hybrid PET scanner based on lutetium yttrium orthosilicate (LYSO) was used to perform PET/CT (Philips Medical Systems, USA). An intravenous injection of ^{18}F-FDG (Cardinal Health, USA) was followed by a PET/CT imaging study 60 minutes later. It is recommended that patients fast for at least six hours before undergoing ^{18}F-FDG PET/CT. Before ^{18}F-FDG was administered, serum glucose levels were less than 110 mg/dl. The area between the cranium and the pelvis, Computed Tomography (CT) was done using the following parameters: 120 kVp, 80 mAs, 16×1.25 mm detector collimation, 1.6 for the beam pitch, 3.75 mm for the section thickness, and 5 mm for the reconstruction pitch (matching the thickness of the PET section). With a 2-minute acquisition time per table location, three-dimensional (3D) whole-body imaging PET data were obtained following CT. In order to reconstruct the images, we used the conventional iterative technique and the ordered subset expectation maximization algorithm (80 mAs low-dose CT) following CT-based attenuation correction. Transaxial, coronal, and sagittal sections were created using a new picture format for three image sets. Utilizing built-in software, PET and CT fusion pictures were obtained.

Nuclear medicine doctor performed the interpretation. On the transaxial, coronal, and vertical sections, the focal FDG uptake zone in the primary tumor was automatically identified as the region of interest (ROI) for calculating SUV (figure 1). SUVmax was the highest SUV for any cross-sectional area, whether it was vertical, coronal, or transaxial. The area within the threshold margin was multiplied by the CT interval to calculate the MTV of each slice.

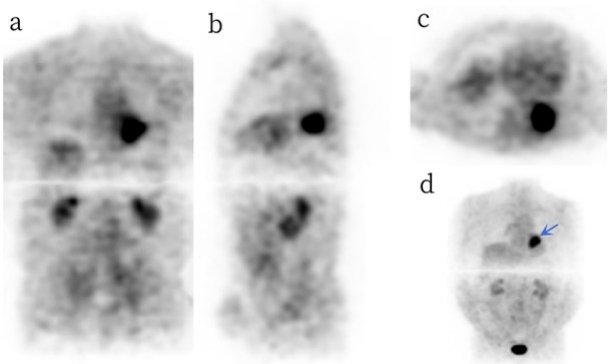

Figure 1. Representative coronal(a), vertical(b), and transaxial (c) positron emission tomography (PET) images of a patient with small-cell lung cancer showing automatically identified the region of interest (ROI) for calculating SUV.

Statistical analysis

Overall survival (OS) and progression-free survival (PFS) outcomes were utilized to evaluate the prognostic value of ^{18}F-FDG PET/CT. OS was calculated as the time from ^{18}F-FDG PET/CT imaging to patient death, regardless of the cause of death. PFS was defined as the period of time between the time of the ^{18}F-FDG PET/CT scan and the occurrence of the initial advancement or the date of any kind of death without an earlier progression.

Models of univariate Cox proportional hazards regression were used to examine factors that could have an impact on tumor prognosis. The determinants of tumor response were found using models of multivariable Cox proportional hazards regression (multivariate analysis included covariates from univariate analysis with $p<0.05$). To illustrate the relationship between PET parameters and clinical outcomes, Kaplan-Meier curves were created. The median value was used as the cut-point to stratify patients into two groups, with separate curves reported by time point. Log-rank tests were performed to compare outcomes between groups. A statistical analysis was conducted using the Statistical Package for Social Sciences, version 20.0 (SPSS Statistics, USA). Statistics were conducted two-sidedly and significance was determined by $p<0.05$.

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RESULTS

The patient and treatment characteristics are shown in table 1. We enrolled and examined all 30 of the eligible individuals. The median age of the cohort was 58 years (range: 39-93), and 86.7% were male. Eighteen (60%) patients were identified as having limited stage. Twenty (66.7%) patients received platinum + etoposide chemotherapy, while 12 (40%) patients received thoracic radiation. The median MTV was 59 mm^3, ranging between 13 and 111 mm^3. A median SUVmax of 11.1 was found in primary tumors (range: 3.4 to 18.1), whereas an SUVmax of 8.1 was found in lymph nodes (range: 3.5 to 12.6).

The median follow-up time was 12 months (6–36 months). A median of 12 months was reported for OS (range: 6–36 months), and a median of 8 months was reported for PFS (range: 5–24 months). Tables 2 and 3 show the univariate and multivariate analysis results. We examined nine factors using univariate Cox proportional hazards regression; MTV and SUVmax of the primary tumor positively affected OS (p=0.01 and 0.046, respectively) and PFS (p=0.001 and 0.049, respectively). Therefore, MTV and SUV^{max} of the primary tumor were included in multivariate Cox proportional hazards regression. Finally, only MTV was related to the OS (p=0.03) and PFS (p=0.014).

The ROC curve depicted MTV's ability to predict tumor prognosis (figure 2). The area under the curve was 0.75, and ROC analysis selected 98 mm^3 as the best cutoff value for MTV. This cutoff value led to two groups of 15 patients: those with MTV values ≤98 mm^3 (low-MTV) and those with MTV values >98 mm^3 (high-MTV). The low-MTV group showed statistically significantly longer OS (p=0.004, figure 3) and PFS (p<0.001, figure 4) than the high-MTV group.

Table 1. Patient characteristics.

Characteristic	No of patients	Percent (%)
Age		
Median	66	
Range	53-82	
Genger		
Male	26	86.7
Female	4	13.3
PS (ECOG)		
0-1	20	66.7
≥2	10	33.3
Tumor stage		
LD	18	60
ED	12	40
MTV		
Median	59	
Range	13-111	
SUVmax of peimary tumor		
Median	11.1	
Range	3.4-18.1	
SUVmax of lymph node		
Median	8.1	
Range	3.5-12.6	
Adjuvant chemotherapy		
Yes	20	66.7
No	10	33.3
concurrent radiotherapy		
Yes	12	40
No	18	60

Table 2. Univariate and multivariate analysis of overall survival.

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	p value	HR (95 % CI)	p value
Age	1.027 (0.890,1.185)	0.713		
Genger male (vs. female)	0.280 (0.025,3.099)	0.3		
ECOG≥2 (vs. 0-1)	25.013 (0.001,2.082)	0.802		
Tumor stage ED (vs. LD)	3.464 (0.169,70.849)	0.42		
MTV	4.297 (1.294,57.989)	0.01	1.042 (1.091,14.996)	0.03
SUVmax of peimary tumor	3.030 (1.420,21.869)	0.046	2.561 (0.886,15.107)	0.068
SUVmax of lymph node	0.976 (0.779,1.223)	0.36		
Adjuvant chemotherapy Yes (vs. No)	0.523 (0.074,3.721)	0.058		
concurrent radiotherapy Yes (vs. No)	1.581 (0.221,11,304)	0.064		
HR = Hazard ratio;CI = confidence interval;ECOG = Eastern Cooperative Oncology Group;				
ED/LD = extensive/limited disease;MTV=metabolic tumor volume;SUVmax = maximum standard uptake value.				

Table 3. Univariate and multivariate analysis of progression-free survival.

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	p value	HR (95 % CI)	p value
Age	0.936 (0.834,1.051)	0.265		
Genger male (vs. female)	0.325 (0.029,3.581)	0.325		
ECOG≥2 (vs. 0-1)	5.309 (0.039,3.783)	0.656		
Tumor stage ED (vs. LD)	2.014 (0.254,15.944)	0.507		
MTV	21.024 (1.858,237.912)	0.001	1.030 (1.063,3.469)	0.014
SUVmax of peimary tumor	1.822 (1.326,10,199)	0.049	3.709 (0.967,6.809)	0.102
SUVmax of lymph node	1.114 (0.934,1.328)	0.23		
Adjuvant chemotherapy Yes (vs. No)	0.904 (0.165,4.970)	0.098		
Concurrent radiotherapy Yes (vs. No)	2.599 (0.475,14.229)	0.071		
HR = Hazard ratio;CI = confidence interval;ECOG = Eastern Cooperative Oncology Group;				
ED/LD = extensive/limited disease;MTV=metabolic tumor volume;SUVmax = maximum standard uptake value.				

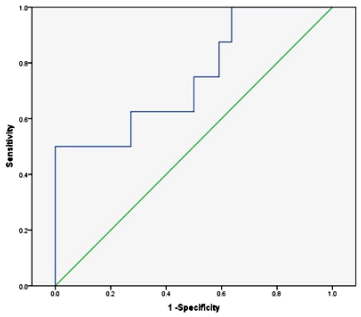

Figure 2. Receiver operating characteristic (ROC) curve using MTV to predict tumor prognosis.

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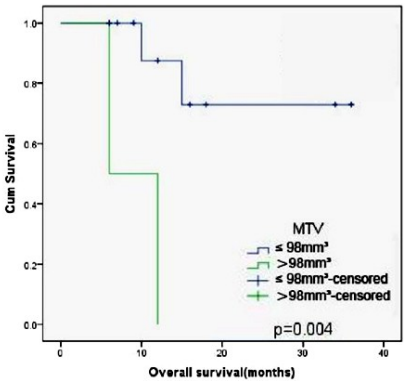

Figure 3. Kaplan-Meier survival curves for overall survival of the two groups according to MTV.

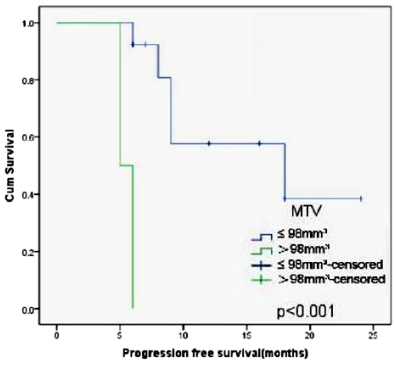

Figure 4. Kaplan-Meier survival curves for progression-free survival of the two groups according to MTV.

DISCUSSION

The use of PET/CT for lung cancer staging and diagnosis has grown. Although similar clinical research has been conducted on NSCLC, due to a lack of research, nothing is known regarding the prognostic value in SCLC. One way to learn about metabolism is to use SUV, a semi-quantitative indicator for tumor ^{18}F-FDG absorption. According to certain research, the SUVmax of the main tumor can be used to predict a patient's prognosis when they have lung cancer [16]. According to a recent study, the survival rate between low and high SUVmax groups was not distinguishably different when the mean SUVmax was divided by 10.4 [17]. For limited-stage SCLC, Gomez *et al.* [18] calculated the median SUVmax for the primary tumor and nodes, as well as the combined median SUVmax for the primary and nodes. They concluded that neither OS nor locoregional recurrence could be predicted by SUVmax. These findings are similar to those of our cohort. According to our study, our study found that SUVmax before initial cancer treatment could not be used as a reliable predictor of survival. There may be a partial volume effect here as well as a correlation between SUVmax and the size of the tumor, but it may also be the result of the limited sample size examined.

Multiple studies have demonstrated an association between OS and MTV in NSCLC patients [19, 20]. SCLC often fails to report volumetric parameters, yet they may provide more accurate prognostic information since they reflect the overall burden of the tumor. According to our research, MTV is a stronger indicator of survival in SCLC patients than the primary tumor SUVmax, because it has a higher association with the outcome. Moreover, patients in the high-MTV group had a poor prognosis than those with a low MTV cut-off value of 98 mm in this retrospective study. These findings were in line with those of Oh *et al.*, who claimed that SCLC patients with high MTV, a measure of systemic tumor load across the body, had a worse prognosis [17]. SCLC patients have experienced considerable toxicity from concurrent chemo-radiotherapy. According to the research, patients with a lower MTV may benefit from further radiation to metastatic areas in the thorax, head, and maybe outside the brain for a better therapeutic response and longer longevity. Our findings imply that FDG PET/CT scans are crucial in aiding treatment choices by offering more specific prognostic data during SCLC initial staging.

Multiple studies have suggested that, besides stage, tumor volume, as assessed by CT, may be a significant predictive factor for survival [21]. Traditionally, tumor size or tumor burden are represented by CT-measured tumor volume. It is important to note, however, that CT-based tumor volumes do not always reflect the true size or burden of tumors since they may contain necrosis and nonviable tissue. A precise reflection of the tumor load is possible thanks to the functional imaging on PET/CT, which can offer metabolic information on malignant tissues. MTV, when used with FDG PET, denotes the volume of tumor tissues having elevated FDG uptake. For some cancers, it has been proposed that SUVmax is a poorer predictive indication than the amount of FDG absorption by tumor tissues, which goes beyond the intensity of FDG uptake (SUVmax) [13,15]. After adjusting for conventional staging, ECOG performance status, treatment regimens, and SUVmax in SCLC patients, the current study shows that MTV, a systemic tumor burden that includes the primary tumor and local lymph nodes, as well as all distant metastases, is a strong independent prognostic factor for death and progression.

Several limitations exist in the current study. First, it is retrospective in nature. Thus, evaluating accurate performance status at the initial stage was also challenging. Second, a consensus is lacking regarding the ideal cut-off value for determining lesion volume. Third, while SCLC is not treated surgically, not all concerned intrathoracic hypermetabolic lesions (i.e., except the primary lesion) were histopathologically confirmed. Therefore, this is an exploratory study.

The findings of our study revealed that MTV, a volumetric measure of ^{18}F-FDG PET/CT, may reliably forecast a patient's prognosis for SCLC. It would be extremely valuable to be able to predict the effectiveness of chemo radiotherapy before the most hazardous portion of the treatment begins. Because metabolic processes take place before significant anatomical changes, ^{18}F-FDG PET imaging can offer more precise prognostic data. Furthermore, to

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validate this finding and enhance the prognosis prediction in SCLC patients, a well-designed, confirmatory validation research with a larger sample size would be required.

CONCLUSION

It is important to identify variables that predict the prognosis of SCLC patients. The MTV of ^{18}F-FDG PET/CT might be utilized as a significant independent predictive factor for OS and PSF in SCLC patients, according to this analysis of our study, which looked at numerous PET measures and controlled for additional clinical variables.

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***Ethical consideration*:** Institutional review board approval was obtained (Ethical Approval NO. 2022-93). Written informed consent was waived by the institutional review board.

***Authors' contribution*:** XC and YH carried out the study concepts and design. Literature research, data analysis and study analysis were done by XC and LS. Manuscript preparation and editing were done by YH and LS. All authors read and approved the final manuscript.

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