

Original Article

Associations between the standardized uptake value of ¹⁸F-FDG PET/CT and demographic, clinical, pathological, radiological factors in lung cancer

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Abstract: Objectives: ¹⁸F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is extensively used to diagnose and stage of lung cancer. The aim of the current study was to investigate the correlation of demographic, clinical, pathological and radiological factors with primer tumor FDG Uptake in patients with lung cancer. Materials and methods: This cross-sectional, clinical study was performed on a total of 57 lung cancer patients newly diagnosed that underwent FDG PET/CT. In addition to descriptive variables, histopathological diagnosis, tumor site and size, hemoglobin level, red cell distribution width, neutrophil to lymphocyte ratio were noted for each patient. The correlation of these variables to SUVmax values in FDG PET/CT was investigated. Results: A total of 57 patients (4 women, 53 men) with an average age of 60.8±9.4 (range: 33-89) participated in the study. Histopathological diagnoses were consistent with squamous cell carcinoma (28, 49.1%), adenocarcinoma (15, 26.3%) and small cell cancer (14, 24.6%). The SUVmax of primary tumor was positively correlated with tumor size (P<0.001). The tumor SUVmax of squamous cell carcinoma (SqCC) (17.49±8.37) was higher than that of adenocarcinoma (AC) (12.80±4.77) and small cell carcinoma (SCC) (12.40±5.80) (P=0.038). Conclusion: SUVmax value was significantly higher for squamous cell carcinoma and its SUVmax values in PET scans was found to be positively correlated with tumor size. This study suggests that, tumor size and histologic subtype had influences upon FDG uptake in lung cancer.

Keywords: Lung cancer, FDG, PET/CT, SUV, neutrophil-lymphocyte ratio

Introduction

Lung cancer is one of the leading causes of cancer concerned death and about 3 million new cases arise annually worldwide [1]. The overall 5-year survival proportions have increased from 12% in the early 70 s to 15% in 2001 [2].

Every pathological stage is composed of a heterogeneous population with individuals at an increased risk for recurrence and death [3]. Hence, identification and usage of noninvasive quantitative measures of biological aggressiveness of lung cancers is important. A better understanding of biological mechanisms involved in lung tumor cells can be helpful and lead

to a better selection of treatment modalities for patients [3, 4].

The introduction of ¹⁸F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) and its use in conjunction with computed tomography (CT) has improved the diagnosis and staging of lung cancer. FDG-PET/CT ensures noninvasive mediastinal staging and thereby decreases the number of futile thoracotomies and mediastinoscopies [2, 3]. Positron emission tomography has a high sensitivity and specificity for the diagnosis of lung cancer compared to CT [2, 5]. It appears to be supplementary to CT and chest X-ray for localization of tumor especially for lesions with poorly demarcated margins [4].

Additionally FDG-PET/CT detects unsuspected extrathoracic metastases in patients otherwise deemed potentially resectable [6]. The number of clinical applications for FDG-PET/CT in lung cancer tends to increase. Moreover, FDG-PET/CT has indicated its value in planning radiotherapy, detection of recurrent disease and identifying tumor response to treatment particularly at an early phase of treatment [1, 7]. Another advantages offered by this technique is that it not only visualizes but also quantifies FDG uptake to allocate metabolically highly active from less active tumor tissues [3, 4].

To the best of our knowledge, demographic, clinical, pathological and radiological factors likely to influence standardized uptake volume in PET have not been clearly documented yet. The present study was implemented to investigate the correlation of clinicopathological parameters with SUVmax in FDG PET/CT of patients with lung cancer.

Patients and methods

Study design

This cross-sectional, clinical study was carried out between in the chest May 2014 and February diseases and nuclear medicine departments of our institution. Both the approval of the local Institutional Review Board and written informed consent from every patient were obtained.

Fifty-six patients (4 women, 53 men) with an average age of 60.8 ± 9.4 (range, 33 to 89) were recruited in this trial. Of these cases, histopathological diagnoses were consistent with squamous cell carcinoma (n=28, 49.1%), adenocarcinoma (n=15, 26.3%) and small cell cancer (n=14, 24.6%). Site of the tumor was defined as peripheral and, central. Tumor size was calculated by multiplication of the height and width in centimeters. According to the tumor (T) size patients were classified as having $T \leq 3$ cm, $3 < T \leq 5$ cm, $5 < T \leq 7$ cm and $T > 7$ cm.

Blood samples have been obtained via peripheral vein puncture from brachial region early in the morning after an overnight fasting period. Uniformly, all the samples were collected in EDTA tubes and transferred to the laboratory for complete blood count analysis including leukocyte (WBC) count, hemoglobin level (Hb), red

cell distribution width (RDW) and neutrophil-lymphocyte ratio (NLR).

Imaging technique

After at least 6 hours of fasting, all patients underwent PET-CT scanning one hour after the intravenous injection of 6-9 mCi (222-33 MBq) F-18 FDG. Whole-body FDG-PET-CT was performed with a combined PET-CT scanner (Biograph mCT 20 Excel, Siemens Medical Solutions, Knoxville TN, USA) with 3-D mod and TOF feature. The emission scans were obtained for 1.5 min per bed position, and transmission scans were obtained with low-dose CT using 100 mA and 120 kvp, 5-mm pitch, 0.5-s tube rotation, 39 mm/sn bed speed, and 512×512 matrix size (skull base to mid thighs). A 3D row-action maximum-likelihood algorithm was adopted for image reconstruction. Region of interests (ROIs) were drawn manually over primary tumor on trans-axial images.

The standardized uptake value (SUV) is defined according to the formula: $SUV = (\text{decay-corrected activity per cc of lesion}) / (\text{injected activity} / \text{patient weight})$, and it was calculated for each serial scan [8].

Outcome parameters

Demographic data (age, gender), hematological indices (Hb level, RDW, WBC count, NLR), tumor site and size, histopathological diagnosis and SUVmax values in FDG PET scans were recorded. Correlation of SUVmax values to these parameters was assessed.

Statistical analysis

Our data was analyzed with IBM Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) Statistics 20 program. The normal distribution of data was tested with Kolmogorov-Smirnov test. Parametric tests were used for variables with normal distribution while non-parametric tests were utilized for analysis of variables that do not exhibit normal distribution. Categorical variables were compared by using Pearson Chi-Square and Fisher's Exact tests. Independent-Samples T test and Mann-Whitney U test were used to compare two independent groups. ANOVA and Kruskal Wallis tests were used to compare more than two independent groups. Correlation between

Table 1. Patient's characteristics

Characteristics		SUVmax mean (± Std. Dev.)	P value
Age	<60 years (n=29)	14.90 (±7.19)	0.911
	>60 years (n=28)	15.12 (±7.56)	
Gender	Male (n=53)	15.08 (±7.44)	0.778
	Female (n=4)	14.00 (±5.96)	
Hb level (g/dl)	<11 (n=17)	14.52 (±7.11)	0.744
	>11 (n=40)	15.22 (±7.47)	
WBC	<10 (n=42)	14.64 (±6.36)	0.528
	>10 (n=15)	16.04 (±9.68)	
Tumor size (cm)	≤3 (n=7)	7.31 (±3.12)	0.006*
	3<T≤5 (n=20)	14.4 (±6.44)	
	5<T≤7 (n=14)	16.7 (±16.7)	
	<7 (n=16)	18.6 (±18.6)	
Pathological type	SqCC (n=28)	17.49 (±8.37)	0.038*
	SCC (n=14)	12.40 (±5.80)	
	AC (n=15)	12.80 (±4.77)	
Tumor localization	Central (n=35)	15.05 (±8.16)	0.778
	Peripheral (n=22)	15.65 (±6.68)	

Abbreviations: SUVmax: maximum standardized uptake volume; Hb: hemoglobin; WBC: white blood cell; AC: adenocarcinoma; SqCC: squamous cell carcinoma; SCC: small cell carcinoma; T: Tumor.

variables was tested with Pearson Correlation test and Spearman Correlation test. Quantitative variables are expressed as either mean ± standard deviation or median-interquartile range. Level of confidence interval was 95%, while P value <0.05 was considered as statistically significant.

Results

A total of 57 patients (4 women, 53 men) with an average age of 60.8±9.4 (range: 33-89) participated in the study. Histopathological diagnoses were consistent with squamous cell carcinoma (28, 49.1%), adenocarcinoma (15, 26.3%) and small cell cancer (14, 24.6%).

As it can be seen in **Table 1**, no significant differences were seen between SUVmax and age (P=0.738), gender (P=0.778), Hb level (P=0.563), RDW (P=0.918), WBC count (P=0.706) and NLR (P=0.765).

There was a positive correlation between tumor size and SUVmax values (Spearman's rho, P<0.001) (**Figure 1**). However, such an association was not detected between SUVmax and tumor localization (variance analysis, P=0.180).

The SUVmax value was significantly higher for squamous cell carcinoma (P=0.038). **Figure 2** demonstrates an example of PET/CT images of a patient with squamous cell lung cancer of lung. **Figure 3** demonstrates an example of PET/CT images of a patient with adenocancer of lung. **Table 2** demonstrates the correlation analysis implemented to investigate any correlation between SUVmax values and parameters under investigation.

Discussion

The current study was sought effect of demographic, clinical, pathological and radiological factors on primer tumor FDG Uptake in patients with lung cancer. SUVmax value in PET/CT scans was found to be positively correlated with tumor size and the SUVmax value was significantly higher for squamous cell carcinoma.

Imaging with FDG-PET/CT is a noninvasive diagnostic method that helps in estimating tumor features. Evaluation of SUVmax measured by FDG-PET/CT is now recognized as a semi-quantitative parameter unique to PET, which is related with tumor aggressiveness in numerous malignancies [9]. Most lung cancers accumulate FDG preferably that SUVmax may vary widely [10, 11]. SUVmax of a tumor is a product of several basic factors including glucose metabolism and the type/number of cells available in the tumor.

The tumor size and the entity of necrosis are other factors that affect the SUVmax of a tumor. Previous studies showed the positive correlation between tumor diameter and SUVmax [12, 13]. The increase in the tumor size was also correlated with more glucose transporter-1 (Glut-1) expression on the surface of tumor cells, leading to increased FDG uptake [16]. In the study by Brown et al, when all histological types are evaluated together the SUV max is positively correlated with the increase of tumor size. However, in respect to histological subtypes the SUVmax is correlated with the tumor sizes in adenocarcinomas though no significant correlation is noted with squamous cell carcinoma.

PET/CT in lung cancer

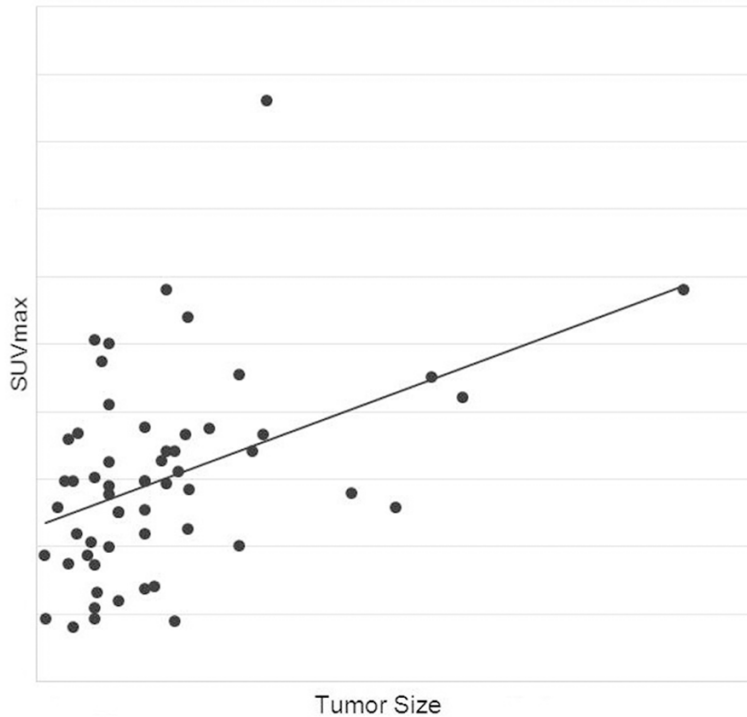


Figure 1. Correlation between tumor size and SUVmax.

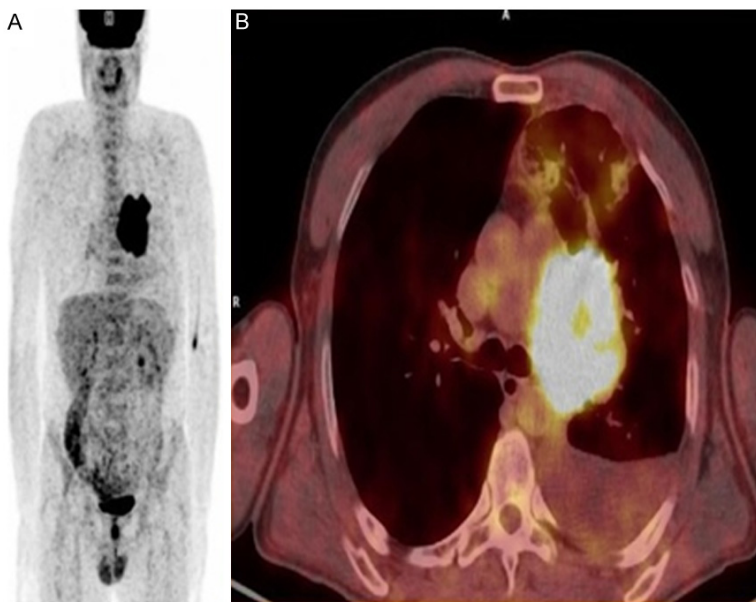


Figure 2. PET/CT images of 62 years old male with squamous cell lung cancer on left lung. SUVmax: 20 A. MIP images of PET C. Fusion PET/CT.

noma and large cell carcinomas [17]. In this study, the tumor size was positively correlated with SUVmax.

In the study of Vessel et al., bronchoalveolar carcinomas, adenocarcinomas, squamous cell

carcinoma and large cell carcinoma histological types were compared in respect to the SUVmax values [18]. According to this comparison, the SUVmax values of bronchoalveolar carcinomas were significantly lower than all other subtypes. In this study, the SUVmax values of adenocarcinomas were also significantly lower than epidermoid and large cell subtypes. No significant difference between epidermoid and large cell carcinomas was identified [19]. In another study, Geus-Oei et al. compared the SUV values of adenocarcinomas, squamous cell carcinoma and large cell carcinomas in a total of 19 NSCLC patients [2]. While the SUV value was significantly higher in squamous cell carcinoma when compared to adenocarcinomas and large cell carcinomas, no significant difference between adenocarcinomas and large cell carcinomas was identified [2]. In our study, the SUVmax value was significantly higher for squamous cell carcinoma.

When the hemoglobin concentration inside RBCs decreases, this also reduces the capacity of the blood to carry oxygen. The mechanism of ^{18}F -FDG accumulation within lung cancer cells is determined by the glucose metabolism, hypoxia and angiogenesis [19]. Hypoxic conditions increase the glucose consumption and the GLUT-1 levels. Enhanced tumor uptake of glucose is facilitated by the overexpression of glucose transporter proteins observed

widely in tumor tissue. Clavo et al. have shown that the SUV values of tumor cells increase in response to hypoxia in various non-lung cancer malign cell samples in their in vitro study [20]. Similar results have also been demonstrated by other researchers [21, 22]. However, some

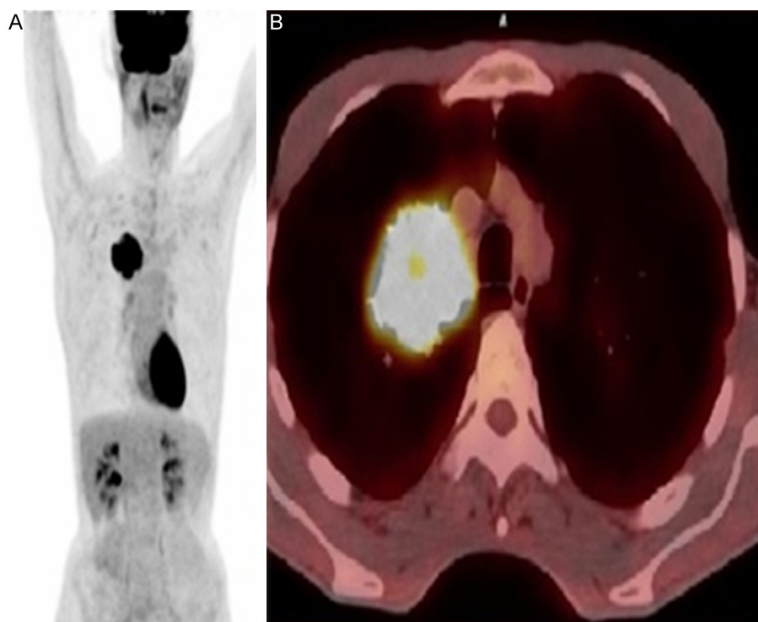


Figure 3. PET/CT images of 52 years old male with adenocancer on right lung. SUVmax; 14.8 A. MIP images of PET C. Fusion PET/CT.

Table 2. Correlation analysis for factors prone to influence SUVmax values in our patients with lung cancer

Variable		Hb	RDW	NLR	WBC	SUVmax
Age	r value	-0.104	0.123	0.040	0.060	-0.450
	p value	0.440	0.362	0.767	0.655	0.738
Hb	r value		-0.652	-0.633	0.025	0.078
	p value		<0.001	<0.001	0.855	0.563
RDW	r value			0.376	-0.021	0.014
	p value			0.004	0.878	0.918
NLR	r value				0.222	0.041
	p value				0.097	0.765
WBC	r value					-0.051
	p value					0.706
Tumor size	r value					0.421
	p value					0.001*

Abbreviations: Hb: hemoglobin; RDW: red cell distribution width; WBC: white blood cell; NLR: neutrophil-lymphocyte ratio; SUVmax: maximum standardized uptake volume *: statistically significant.

the data on lung cancer is controversial. Pederson et al. have shown that the SUV value increases after exposure to acute hypoxia in SCLC series in in vitro and in vivo animal trials [23]. Cherk et al. have stated that hypoxic areas demonstrated less FDG enhancement and that no correlation was present between hypoxia and the SUV values [24]. In our study, the SUVmax values of patients with and without

low hemoglobin concentrations were no different.

Inflammation has a critical role in tumorigenesis [25], from initiation, promotion, malignant conversion, invasion, and metastatic progression [26]. Inflammatory conditions can be present either before or after a malignant change occurs. Inflammatory cells like activated granulocytes, lymphocytes, and macrophages are well known to have increased glycolysis due to the high amount of glucose transporters [27-29].

Elevated neutrophil to lymphocyte ratio (NLR) was found to predict a shorter survival in patients with advanced lung cancer. It is an easily measured, reproducible test that could be considered to be incorporated in the routine practice in lung cancer patients [30]. However, we came across no significant correlations between NLR and these parameters.

FDG accumulation in the primary site of early stage lung cancer is mainly detected by tumor histopathology and the combination of the expression level of the glucose membrane transporters as well as tumor cell differentiation. This demonstrate that sufficient FDG uptake capability is linked with these transporters [31]. Additionally, the present study indicated a relationship

between FDG uptake and histopathology of the tumor, as the SUV was significantly higher in squamous cell carcinomas compared to adenocarcinomas or large cell carcinomas. It appears that more aggressive neoplasms or neoplasms with poorer prognosis, demonstrate higher levels of glucose transporter expression on the cell membrane of tumor cells and thus indicate a higher level of FDG accumulation [32].

The prognostic significance of FDG uptake has been indicated in patients with lung cancer [5]. Uptake of FDG was consistently found to be an independent prognostic marker. Further trials with longer follow-up durations may clearly elucidate the clinical usefulness of FDG-PET/CT in staging lung cancer precisely [5]. It should be emphasized that such algorithms are system specific and that the whole chain from the PET system to the treatment must be strictly kept under control when used in clinical practice [33].

Some limitations of the current study must be emphasized. First, this study was executed on a relatively small sample size and heterogeneity in terms of histopathological diagnosis constitutes an important restriction for interpretation of our results. In addition, many factors such as environment, genetics, economical status and ethnicity may influence the FDG uptake. Lack of analysis of factors like tumor differentiation, total lesion glycolysis and SUVmean constitute other limitations for this trial.

In conclusion, SUVmax value in PET scans was significantly higher for squamous cell carcinoma and it was found to be positively correlated with tumor size. This study suggests that, tumor size and histologic subtype had influences upon FDG uptake in lung cancer.

Disclosure of conflict of interest

None.

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