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FDG-PET/CT tumor to liver SUV ratio (TLR), tumor SUV_{max}, and tumor size: can this help in differentiating squamous cell carcinoma from adenocarcinoma of the lung?

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Abstract

Background: PET/CT plays an essential role in the diagnosis, staging, and follow-up of lung cancer. We aimed to assess the ability of PET/CT to differentiate between adenocarcinomas (AC) and squamous cell carcinomas (SCC) of the lung using tumor size, tumor maximum standardized uptake value (SUV_{max}), lymph nodes SUV_{max}, and tumor to liver SUV ratio (TLR).

Results: A total of 60 patients pathologically proved to have non-small cell lung cancer either AC or SCC were retrospectively evaluated. The mean tumor size, SUV_{max} of the tumor, and TLR were significantly higher in SCC lesions compared to AC lesions. The mean SCC tumoral size was 7.96 ± 2.18 cm compared to 5.66 ± 2.57 cm in AC lesions ($P = 0.008$). The mean tumor SUV_{max} in SCC lesions was 18.95 ± 8.3 compared to 12.4 ± 7.55 in AC lesions ($P = 0.04$). While the mean TLR of SCC lesions was 10.32 ± 4.03 compared to 7.36 ± 4.61 in AC lesions ($P = 0.028$). All three parameters showed the same sensitivity (75%), while TLR showed the highest specificity (77.78%) followed by tumor size (76.47%) and then SUV_{max} of the tumor (72.22%).

Conclusions: SCC of the lung has a higher mean tumor size, SUV_{max} of the tumor, and TLR as compared to AC which can be helpful tools in differentiation between them using PET/CT.

Keywords: NSCLC, Adenocarcinoma, Squamous cell carcinoma, PET/CT, SUV_{max}, TLR

Background

Lung cancer is considered one of the commonest cancer in the world characterized by its high mortality rates worldwide [1, 2]. Pathologically, bronchogenic carcinoma has two major types namely; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) with NSCLC being the commonest type representing 86% of cases. NSCLC is further subdivided into three main subtypes with adenocarcinoma (AC) that comes with the highest incidence (60%) followed by squamous cell carcinoma (SCC) (20%) and lastly large-cell carcinoma (3%) [3].

The integration of Fluoro-deoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) plays an essential role in the diagnosis and staging which reflects on the treatment strategy and follow-up of patients with bronchogenic carcinoma. PET/CT is a well-established radiological modality with high diagnostic accuracy in metastases detection compared to usual CT. Also, it has been reported that up to 10% of patients with bronchogenic carcinoma are found to have metastases on PET/CT that were not detected on CT with subsequent different patients' staging [1]. The high accuracy of PET/CT in tumor staging makes it important for the

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treatment strategy either surgical treatment or radiotherapy or chemotherapy. Also, it becomes essential during the follow-up to detect recurrence. PET/CT shows a higher ability to evaluate the early response to the treatment as chemotherapy by its ability to detect the metabolic response even before the size change [4].

SUV_{max} is a PET semi-quantitative index that is calculated easily and considered a reflection of the lesion metabolic activity. It is a well-known parameter used to differentiate malignant from benign lesions [5].

It is important to differentiate AC from SCC of the lung because this affects the management strategy of the patients and changes the choice of treatment type. For example, Pemetrexed is known to have more effect during the treatment of patients with advanced lung AC rather than SCC. Also, Bevacizumab used in the treatment of patients with AC is considered contraindicated in patients with SCC [6].

The most standard way of differentiating the different types of bronchogenic carcinoma is tissue biopsy. In cases of peripheral tumors, CT-guided biopsy is the method of choice but it carries a risk of pneumothorax and pleural effusion/hemorrhage [7]. However, in cases with central masses, it is recommended for the biopsy to be taken trans-bronchial, but this carries the risk of hemorrhage secondary to vascular/tissue injury especially if close to the mediastinal structure [8].

Because of biopsy complications, it is important to search for other non-invasive modalities to differentiate the different pathological types of lung cancer to avoid such complications and decrease the incidence of patient morbidity and mortality secondary to biopsy. Recent research is now directed to the use of PET/CT not only in the diagnosis, staging, and follow-up of patients but also to differentiate between different histological subtypes and also with different tumor grades [9–14].

In this study, we tried to assess the ability of PET/CT as a non-invasive radiological modality that can be used to differentiate AC from SCC by comparing the tumor size, tumor SUV_{max}, and lymph nodes SUV_{max}, and tumor to liver SUV_{max} ratio (TLR).

Methods

Patient selection

After ethical approval from our institutional ethical committee, 60 patients with pathologically proved NSCLC were included in this retrospective study who came in the period from April 2018 to December 2020 to do PET/CT in Radiology Department-Ain Shams University after a referral from the chest/radiotherapy team for staging aiming to start the adequate therapy or to proceed with surgery if indicated. The patient's privacy and data confidentiality were guaranteed during the whole study. All patients were subjected to post-contrast CT followed by PET scanning in the same session.

We included any patient with biopsy proved AC or SCC before starting any type of treatment related to lung cancer. No age or sex predilection. We excluded any patients with unavailable pathological data or cases with other pathological types rather than SCC or AC. Also, patients who came for follow-up studies after the start of treatment were excluded to avoid the effect of treatment on the tumor size and metabolic activity.

Patient preparation

Scans were scheduled at least one month after any tumoral/nodal biopsy to avoid false-positive results. All patients were instructed to avoid vigorous exercise for several days before scanning, to fast except water for 4–6 h at least before the examination. Recent serum creatinine was requested and confirmed to be within normal before the study. Also, in cases with diabetes adequate control of the blood glucose level was required before the date of imaging with serum glucose levels were measured to ensure adequate glucose level (Fasting blood glucose level < 150 mg/dl).

Venous access was needed with the insertion of a cannula inside the antecubital vein was preferable at the contralateral tumor side. The patients were kept in a controlled warm temperature room to decrease the FDG uptake by the brown fat.

PET/CT technique

We used a Discovery IQ 5 ring machine class I IPX0 with 16 slices CT, GE (General Electric Company, Milwaukee, Wisconsin, USA, 2016). 10–20 mCi were injected 45–60 min before the exam and the patients were asked to rest in a quiet place without vigorous activity and trying to avoid even talking as minimal as they can.

All patients were placed in a supine position with elevated arms for imaging acquisition starting from the skull vault down to the upper thigh level. We started with post-contrast CT followed by PET imaging using the same scan area.

125 mL of a low-osmolarity contrast medium was used for CT imaging (Optiray 350) at a rate of 4 mL/s by using an injector. The scanning parameters were 110 mA, 110 kV, 0.5 s tube rotation time, and 3.3 mm section thickness. This was followed immediately by PET scanning using the same field of view with six to seven-bed positions planned in the three-dimensional acquisition mode. Three to five minutes were consumed for each acquisition at each bed position.

The patients were asked to avoid children for at least 24 h after the study, drink plenty of amounts of water, and stop lactation for 24 h.

Image interpretation

All images including PET and CT images were transferred to a specific workstation where PET/CT fused images could be done. Multi-planar reformatted images (MPR) were done for both PET and CT images. PET/CT images were interpreted via an experienced specialized radiologist in PET/CT fields for at least five years blinded to the pathological types of the cases.

The size of the tumor was measured as the maximum diameter of the lesion measured in the contrast-enhanced CT images. SUV_{max} of the tumor was measured by placing the region of interest (ROI) around the primary tumor that has avid FDG uptake. SUV_{max} of the LN was measured by placing the ROI around the lymph node that has avid FDG uptake. SUV_{max} of the liver was measured by placing the ROI at the liver. TLR was calculated by dividing the SUV_{max} of the tumor by the SUV of the liver.

Statistical analysis of data

The analysis of data was done using IBM SPSS statistics (V. 24.0, IBM Corp., USA, 2016). Wilcoxon–Mann–Whitney test was used to compare the means of quantitative variables for two independent groups. The Chi-square test was used to compare the two independent groups regarding qualitative data. Spearman correlation coefficient was used to determine the correlation between quantitative variables. Receiver operating characteristics (ROC) and area under the curve (AUC) were used to determine the ability of a quantitative variable to differentiate between two independent groups with a determination of the cut-off with the best sensitivity and specificity.

Results

This was a retrospective study conducted over 60 patients with a mean age of 56.9 ± 11.5 years. 50 patients were males representing 83.3% with a mean age of 56.28 ± 11.54 years while the rest 10 patients representing 16.7% were females with a mean age of 60 years ± 12.27 years. 36 patients (60%) were diagnosed by a biopsy to have AC while the rest 24 patients (40%) were diagnosed with SCC.

We found no significant relationship between the histopathology of the tumor and the age or the sex of the patients *(P value* = 0.55 *and* 0.32, *respectively)* (Table 1).

As regards the bronchogenic carcinoma tumoral mass size, the mean tumor size was 6.58 ± 2.65 cm in all our cases. The tumoral mass size showed a statistical significance higher difference between the patients with SCC measuring 7.96 ± 2.18 cm compared to the size in patients with AC measuring 5.66 ± 2.57 cm with a calculated *P value* = 0.008 (Tables 1, 2) (Fig. 1). There was no significant relationship between the size of the tumor and the age or sex of the patients *(P value* = 0.27 *and* 0.53, *respectively)* (Table 1).

The mean SUV_{max} of the tumor between our 60 patients was 15.02 ± 8.4 (range: 2–32.8). The mean SUV_{max} of AC lesions was 12.4 ± 7.55 (range: 2–32.8), while the mean SUV_{max} of SCC lesions was 18.95 ± 8.3 (range: 3.7–30.77). The mean SUV_{max} of lesions in patients with SCC was significantly higher than that of patients with AC using the Wilcoxon–Mann–Whitney test *(P value* = 0.04*)*

Table 1 Shows the *P* value of different relations and correlations between different variables in our study

Variable	Age	Sex	Pathology	Size	SUV_{max} (T)	TLR	SUV_{max} (LN)
Age		0.49	0.55	0.27	0.87	0.51	0.67
Sex	0.49		0.32	0.53	0.16	0.25	0.73
Pathology	0.55	0.32		0.008	0.04	0.028	0.53
Size	0.27	0.53	0.008		0.03	0.66	0.13
SUV_{max} (T)	0.87	0.16	0.04	0.03		0.000	0.000
TLR	0.51	0.25	0.028	0.66	0.000		0.044
SUV_{max} (LN)	0.67	0.73	0.53	0.13	0.000	0.044	

Correlation is significant at the 0.05 level.
Correlation is highly significant at the 0.01 level.

(T) Tumor lesion
(TLR) Tumor-to-liver ratio
(L.N) lymph node

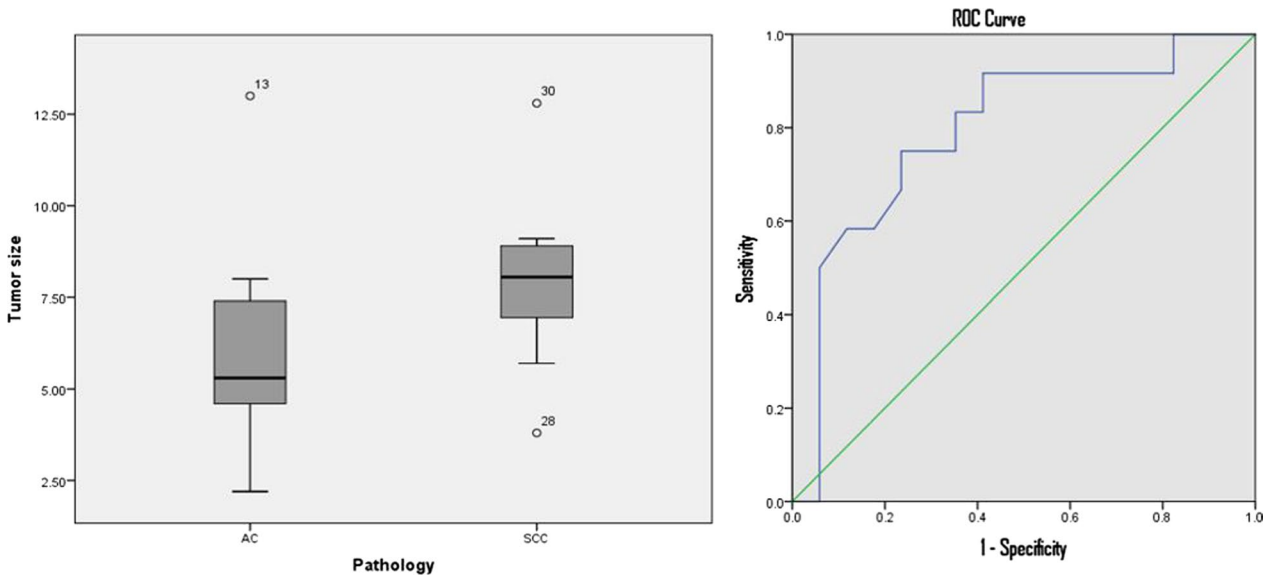

Fig. 1 Comparison of tumor size (Max diameter) of the lesion between AC and SCC. Also, the ROC curve of the size of the lesion concerning the histopathology of the lesion

Table 2 Shows the mean size of the tumor including the standard deviation, and range based on the histopathological types

Mean size of the tumor							
Histopathology	**Number**	**Mean size of the tumor**	**Std. deviation**	**Range**	**Minimum**	**Maximum**	**Std. error of mean**
AC	36	5.6611	2.57480	10.80	2.20	13.00	.60689
SCC	24	7.9583	2.18318	9.00	3.80	12.80	.63023
Total	60	6.5800	2.64659	10.80	2.20	13.00	.48320

(Tables 1, 3) (Figs. 2, 3, 4). There was no statistically significant difference found between the SUV_{max} of the tumor and the sex of the patients *(P value* = 0.16*)*. Also, we found no significant relationship between the SUV_{max} of the lesion and the age of the patients *(P value* = 0.87*)* (Table 1).

Between the 60 patients, 45 patients showed positive metastatic lymphadenopathies with no statistically significant difference between the AC and SCC in lymph nodes SUV_{max} *(P value* = 0.53*)*. While we found a highly significant correlation between the SUV_{max} of the LN and the SUV_{max} of the tumor and only a significant correlation with the TLR (Table 1) (Figs. 5, 6).

Lastly, the SUV_{max} of the tumor was divided by the SUV of the liver to calculate the tumor to liver ratio (TLR). The mean TLR of the 60 patients was 8.54 ± 4.56 (range 1.43–21.5). The mean TLR of AC patients was 7.36 ± 4.61 (range 1.43–21.5) while it was 10.32 ± 4.03 (range 2.68–16.69) for SCC patients. A statistically significant difference was found between patients with AC and SCC as regards the TLR *(P value* = 0.028*)* with TLR tended to be higher in patients with SCC (Tables 1, 4) (Figs. 3, 4, 5, 6, 7). A significant relation was found between TLR and SUV_{max} of the tumor *(P value* = 0.000*)*. No significant relation was found between the TLR and the size of the lesion *(P value* = 0.66*)* (Table 1).

The best cut-off value in our study regarding the tumor mass size was 7.55 cm with 75% sensitivity, 76.5% specificity, and area under curve = 0.794 (Table 5) (Fig. 1). while for SUV_{max} was 15.45 with 75% sensitivity, 72.2% specificity, and 73.3% accuracy, and area under curve = 0.72 (Table 5) (Fig. 2). The best cut-off value of TLR to be used as a differentiation between the AC and SCC was 9.49 with 75% sensitivity, 77.8% specificity, and 76.67% accuracy, and area under curve = 0.741 (Table 5) (Fig. 7).

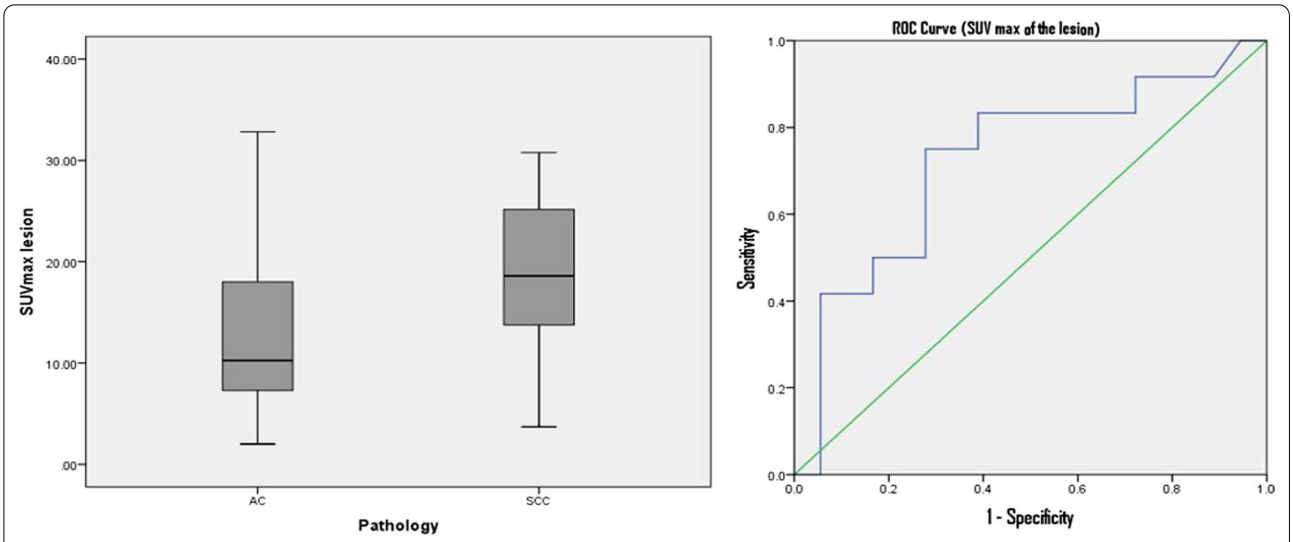

Fig. 2 Comparison of SUVmax of the lesion between AC and SCC. Also, the ROC curve of the SUV max of the lesion concerning the histopathology of the lesion

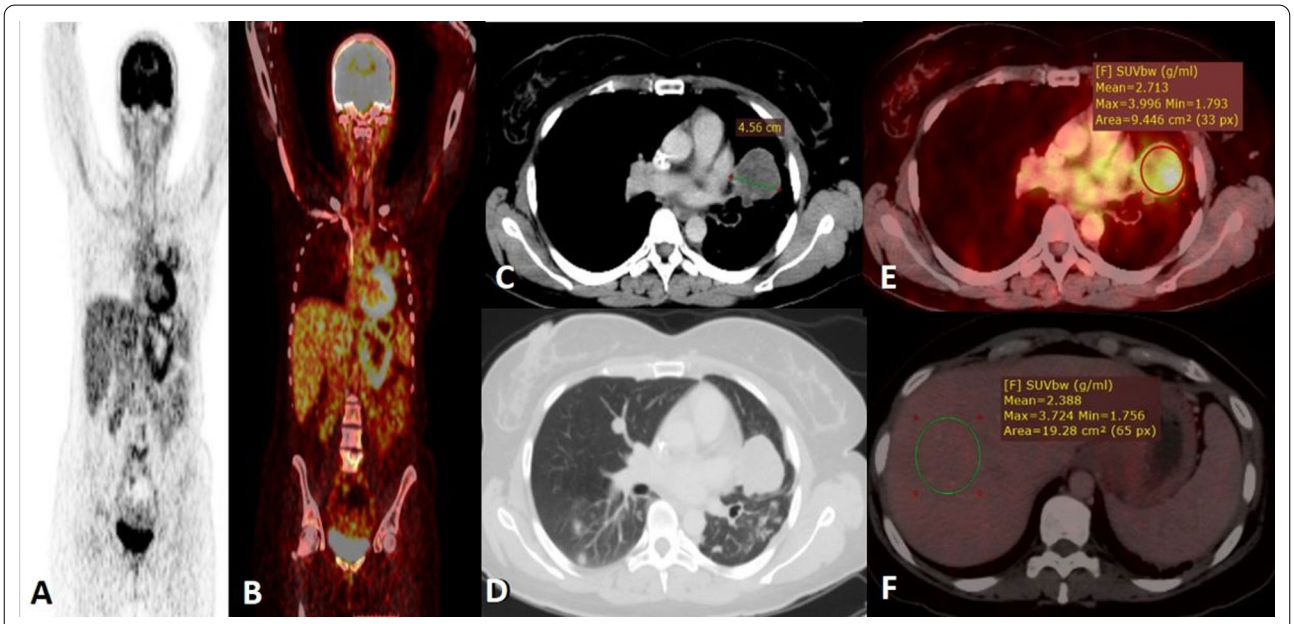

Fig. 3 A 52-year-old female patient proved histopathologically to have adenocarcinoma (AC) involving the left upper lobe. **A** (coronal PET), **B** (coronal PET/CT), **C** (axial CT in a mediastinal window), **D** (axial CT in a lung window), **E** and **F** images (axial PET/CT images). The mass lesion size measured in the **C** image was 4.56 cm with SUVmax of the tumor was 3.99 as shown in **E**. TLR was calculated to be 3.99/3.72 = 1.07

Discussion

In this study, we tried to differentiate between AC and SCC of the lung using PET/CT parameters. We found a statistically significant difference between the SCC and AC regarding the tumor size, SUV_{max} of the tumor, and the TLR with these parameters are higher among patients with SCC.

We studied 60 patients who were pathologically proven to have either lung SCC or AC which are considered the most common pathological types. The number of patients with AC was larger than patients with SCC at 60% and 40%, respectively. This is consistent with the international epidemiology of lung cancer and the switch that happened after 1990 with lung AC becoming the

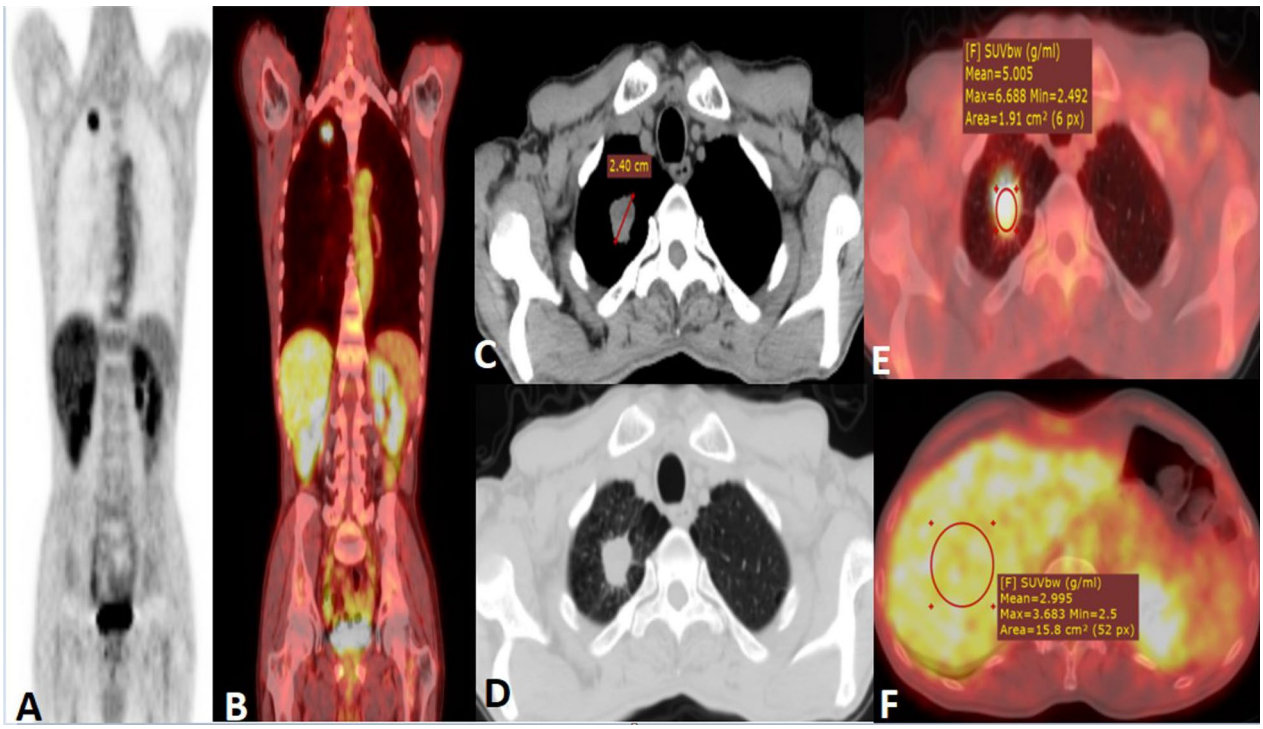

Fig. 4 A 56-year-old male patient proved histopathologically to have adenocarcinoma (AC) involving the right upper lobe. **A** (coronal PET), **B** (coronal PET/CT), **C** (axial CT in a mediastinal window), **D** (axial CT in a lung window), **E** and F images (axial PET/CT images). The mass lesion size measured in the **C** image was 2.4 cm with SUVmax of the tumor was 6.69 as shown in **E**. TLR was calculated to be 6.69/3.72 = 1.79

Table 3 Shows the mean SUV_{max} of the tumor including the standard deviation, and range based on the histopathological types

Mean SUV_{max} of the tumor							
Histopathology	**Number**	**Mean SUV_{max} of the tumor**	**Std. deviation**	**Range**	**Minimum**	**Maximum**	**Std. error of mean**
AC	36	12.3989	7.55340	30.80	2.00	32.80	1.78035
SCC	24	18.9558	8.29885	27.07	3.70	30.77	2.39567
Total	60	15.0217	8.38111	30.80	2.00	32.80	1.53018

first type of lung cancer representing 60% of all types followed by SCC representing 20% [3]. Karam et al. [12], Kim et al. [13], and Wang et al. [14] also included patients with only pathologically proven AC and SCC during their research and found that the AC patients are more than SCC patients; AC patients in their sample represented 60.2%, 56.3%, and 66.4%, respectively, which is very close to our patient sample. However, Lu et al. [15] and Sunnetcioglu et al. [16] included patients with other pathological types such as bronchoalveolar carcinoma and small cell lung cancer.

A significant correlation was found between the size of the tumor measured on contrast-enhanced CT images and the pathological type of the tumor with SCC masses showed higher sizes compared to the AC masses with *P* value = 0.008. This is also in keeping with previous studies that found a larger size of SCC tumor [12, 14, 17].

Multiple previous studies found a significant correlation between the pathological type of the NSCLC and SUV_{max} of the tumoral lesions with SCC lesions showed higher SUV_{max} compared to AC [12–17]. This is in agreement with our result and this can be explained by the higher size of the SCC tumors as shown in our study and subsequently containing a larger number of malignant cells leading to increased metabolic activity compared to AC tumors which reflects the FDG uptake and SUV_{max}.

De Geus et al. [18] found a significant difference between the SUV_{max} of SCC compared to AC and large

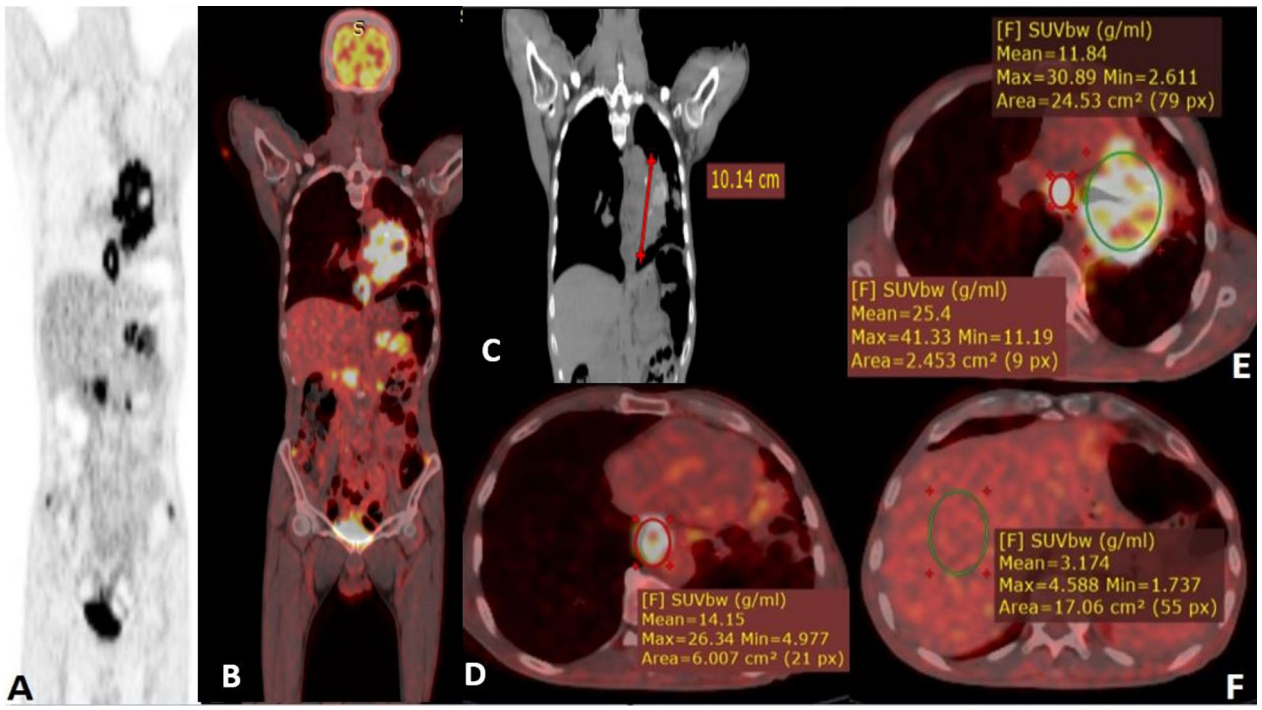

Fig. 5 A 59-year-old male patient proved histopathologically to have squamous cell carcinoma (SCC) involving the left upper lobe. **A** (coronal PET), **B** (coronal PET/CT), **C** (coronal CT in a mediastinal window), **D**, **E**, and **F** images (axial PET/CT images). The mass lesion size measured in the **C** image was 10.1 cm with SUVmax of the tumor was 30.9 as shown in **E**. TLR was calculated to be 30.9/4.58 = 6.75. Para-esophageal (**D**) and Subcarinal (**E**) lymphadenopathies noted with SUVmax = 26.34 and 41.33, respectively

cell carcinoma yet there was no significant difference found between AC and large cell carcinoma. Lu et al. [15] found a statistically significant difference between the SUV_{max} of SCC, AC, and bronchoalveolar carcinoma. Multiple studies also found a correlation between the SUV_{max} and the degree of differentiation of the tumor [9, 17].

No statistically significant correlation was found between the SUV_{max} of the tumor and the sex or gender of our patients and this is consistent with Karam et al. [12] and Lin et al. [19].

Regarding the SUV_{max} of the lymph nodes, no significant difference was found between the SUV_{max} of the lymph nodes of AC patients and SCC patients and no significant correlation between the SUV_{max} of the lymph nodes and the size of the tumor; however, we found a highly significant correlation between the SUV_{max} of the LN and SUV_{max} of the tumor. Wang et al. [14] also found no difference between AC and SCC as regards the metastatic lymph nodes SUV_{max}. Nambu et al. [20] and Li et al. [21] reported that tumor with higher SUV_{max} has a higher risk of lymph nodes metastases.

In the current study, we tried to make a normalization for the SUV_{max} of the tumor by dividing it by the SUV_{max} of the liver trying to eliminate the effects of other parameters that may affect the accuracy of the SUV_{max} such as the dose of FDG, the weight of the patient, the time gap between the injection and the acquisition and lastly the patients' glucose level. Multiple previous types of research used the liver as a parameter for normalization [17, 22]. TLR showed a significant difference between patients with AC and patients with SCC being higher in patients with SCC and this is consistent with Duan et al. [17] who concluded that TLR is one of the parameters which can be used to differentiate between SCC and AC and also showed a significant correlation with the tumor differentiation.

To our knowledge, no previous studies tried to calculate the cut-off values of SUV_{max} of the tumor, size of the tumor, and TLR which can be used to differentiate between the SCC and AC. However, all these parameters showed the same sensitivity (75%), and TLR showed the highest specificity 77.78% compared to 76.47% for tumor size and 72.22% for SUV_{max}.

Shao et al. [23] tried to use PET/CT to predict the different pathological subtypes and growth patterns of early adenocarcinoma. They found higher SUV_{max} in cases with invasive adenocarcinoma compared to adenocarcinoma in situ and minimally invasive adenocarcinoma with median $SUV_{max} = 2.0$ which was the optimal cutoff

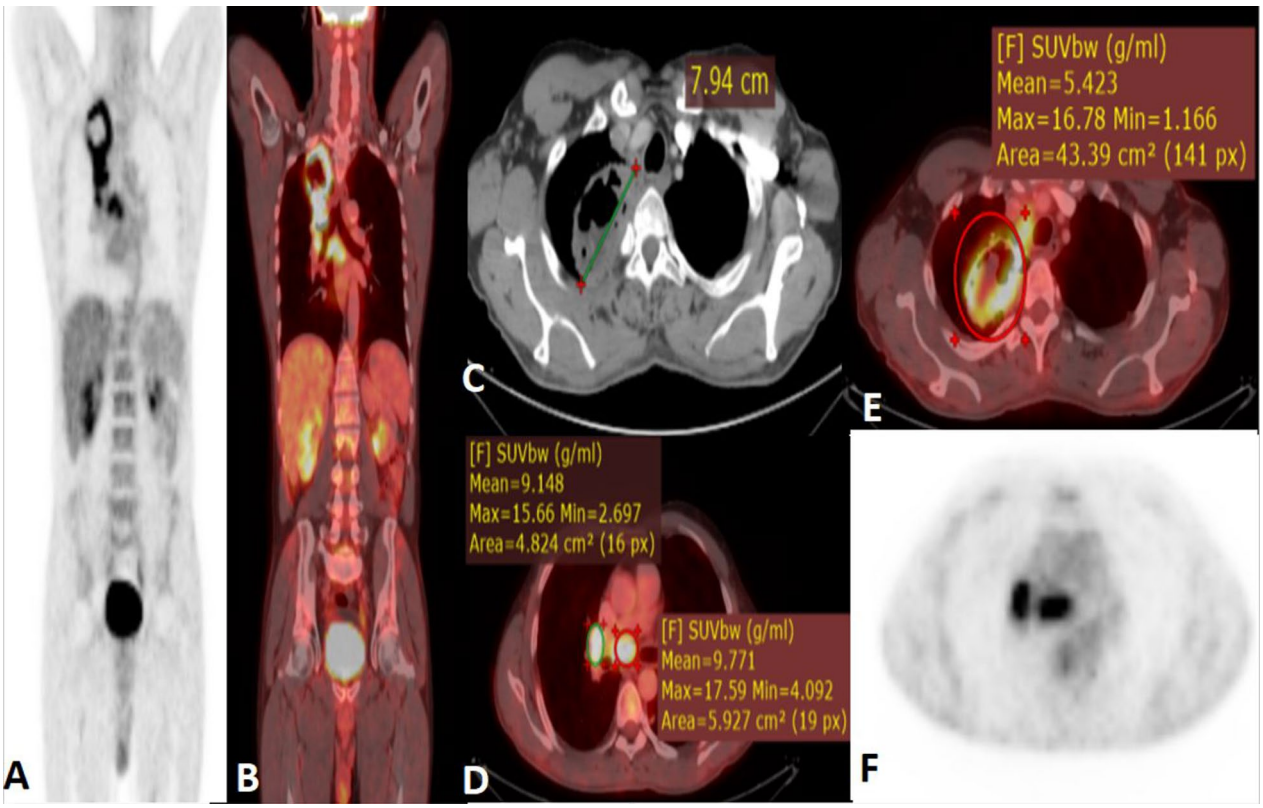

Fig. 6 A 61-year-old male patient proved histopathologically to have squamous cell carcinoma (SCC) involving the right upper lobe. **A** (coronal PET), **B** (coronal PET/CT), **C** (axial CT in a mediastinal window), **D**, **E** (axial PET/CT images), **F** (axial PET). The mass lesion size measured in the **C** image was 7.94 cm with SUVmax of the tumor was 16.78 as shown in **E**. TLR was calculated to be 16.78/1.65 = 10.17. Right hilar and subcarinal lymphadenopathies were noted (**D** and **F**) with SUVmax = 15.66 and 17.59, respectively

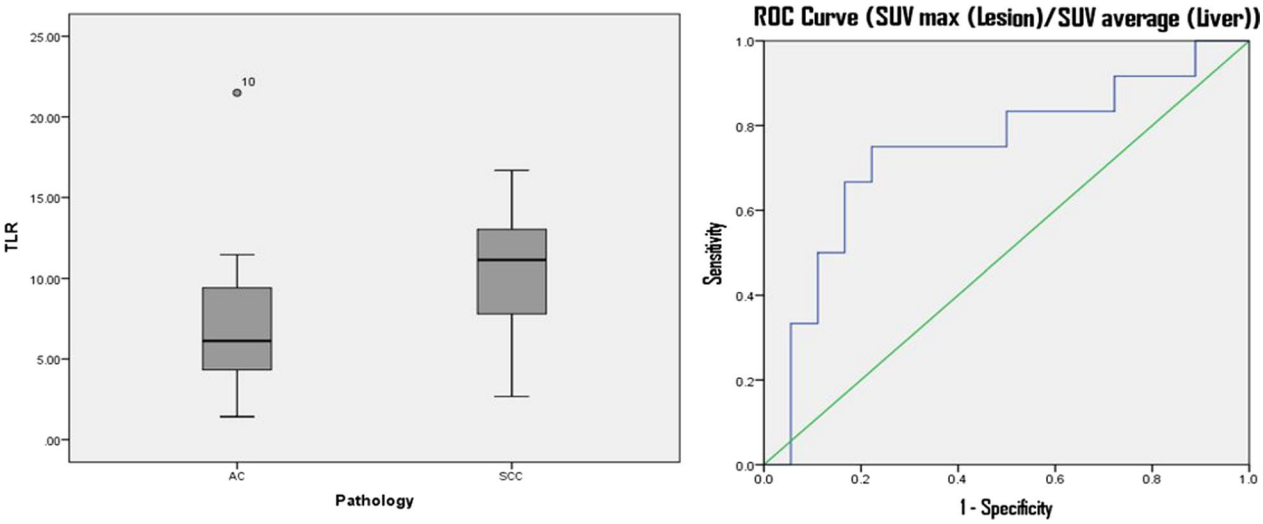

Fig. 7 Comparison of TLR between AC and SCC. ROC curve of the tumor-to-liver ratio (TLR) concerning the histopathology of the lesion

Table 4 Shows the tumor to the liver ratio (TLR) including the standard deviation, and range based on the histopathological types

Mean TLR							
Histopathology	**Number**	**Mean TLR**	**Std. deviation**	**Range**	**Minimum**	**Maximum**	**Std. error of mean**
AC	36	7.3579	4.61070	20.07	1.43	21.50	1.08675
SCC	24	10.3188	4.02742	14.01	2.68	16.69	1.16262
Total	60	8.5422	4.55972	20.07	1.43	21.50	.83249

Table 5 Shows the cut-off values of different variables including the size of the tumor, SUV_{max} of the tumor, and TLR used to differentiate between AC and SCC demonstrating the diagnostic performance of these cut-off values

Variable	**Best cut-off value**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**	**LR+**	**LR−**
Size (Max diameter)	7.55	75	76.47	69.23	81.25	75.86	3.19	0.33
SUV_{max} (Lesion)	15.45	75	72.22	64.29	81.25	73.33	2.7	0.35
TLR	9.49	75	77.78	69.23	82.35	76.67	3.38	0.32

value with P value = 0.008. Also, they found a SUVmax of 1.4 was the optimal cutoff value for differentiating the growth pattern of adenocarcinoma.

Liu et al. [24] tried to use SUVmax to differentiate between the synchronous multiple primary lung tumors and the lung metastases and they found SUVmax of 1.7 the best cut-off value with 62.7% sensitivity and 82.6% specificity.

Limitations The current study tried to differentiate between the two commonest pathological subtypes of lung cancers. So, further studies can be conducted on more pathological types. Also, bigger sample size and multicentric studies are needed to obtain more accurate results. Finally, the degree of tumor differentiation is better to be added in comparison.

Conclusions

PET/CT is the gold standard for lung tumor staging with tumor SUV_{max}, TLR, and tumor size can be used as non-invasive quantitative differentiation parameters between SCC and AC being higher among SCC. With more advances in PET/CT, biopsy hazards are expected to be avoided.

Abbreviations

AC: Adenocarcinoma; CT: Computed tomography; FDG-PET: Fluoro-deoxy-glucose positron emission tomography; LR+: Positive likelihood ratio; LR−: Negative likelihood ratio; NPV: Negative predictive value; NSCLC: Non-small cell lung cancer; PPV: Positive predictive value; ROC curve: Receiver operating characteristic curve; SCC: Squamous cell carcinoma; SCLC: Small cell lung cancer; SPSS: Statistical package forth social sciences; SUV_{max}: Maximum standardized uptake value; TLR: Tumor-to-liver ratio.

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Author contributions

AMAS and AMO shared in writing, editing, data collection, statistical analysis of the research in almost the same way. AMO was responsible for PET/CT interpretation while AMAS was responsible for pathological results collection. LHH was the supervisor and revised all our steps and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate were taken from our institute ethical committee (Faculty of Medicine-Ain shams university) with written informed consents were waived being a retrospective study.

Consent for publication

The written informed consents were waived being a retrospective study.

Competing interests

The authors declare that they have no competing interests.

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