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RESEARCH ARTICLE

The Role of PET-CT-Scan in Evaluation of Bronchogenic Carcinoma in Iraq

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ABSTRACT

Currently, fluorodeoxyglucose (FDG) positron emission, its importance has been increasingly in lung cancer. Previous studies and literatures have demonstrated the superior accuracy of FDG-PET than CT-scan in diagnosis, and staging of lung cancers. Nonetheless, still a disadvantage of FDG-PET, in anatomical localization of the pathology. In Iraq, studies concerned with the evaluation of FDG-PET are almost unavailable. Assess the utility of PET-CT in patients with bronchogenic carcinoma for the following: Staging of the bronchogenic carcinoma in Iraq and Follow up of the patients with bronchogenic carcinoma after treatment. This prospective study was involved 100 patients. All patients were referred for PET-CT- scan which are proved by biopsy as Non small lung carcinoma for initial staging with Fluorine-18 fluorodeoxyglucose–Positron Emission Tomography–Computed Tomography- SCAN, out of 100 patients 12 patients followed by another FDG –PET- CT- SCAN six months later after treatment to assess regression or progression of the tumor. Our patients were biopsied either by bronchoscope or CT guided Tru- cut biopsy in Al-Sader medical city in Al- Najaf – radiology department between February 2021- February 2022. The FDG PET –CT SCAN preformed at Amir AL-Momineen speciality hospital oncology & nuclear medicine center. The patients median age was 60 (range 36 – 90) years, and 69% of the patients were older than 50 years. Males represented 70%. Shortness of breath was the main complaint. Secondary lesions reported in 14 cases and were cited in liver, MSK, supra renal gland, and right kidney. Lymphadenopathy (LAP) reported in 37 cases. The mean Standardized Uptake Values was significantly increased with advancing stage, (P. value <0.05). Receiver operating characteristic curve analysis revealed that SUV was good predictor of advanced stage of malignancy, at an optimal cutoff point of 10.5 (SUV). PET -CT –Scan appears to have an important role and performance in evaluation and staging of bronchogenic carcinoma, PET -CT –Scan demonstrated high performance in detection of mediastinal nodal and distant metastasis, and At cutoff value of SUV of 10.5, PET -CT –Scan produce high sensitivity, specificity and accuracy of more than 85%, with low false positive and false negative rates.

INTRODUCTION

Lung cancer significantly constitutes the major cause of deaths around the world among both men and women, which in the United States in 2018, there were an average 234 030 cases reported of lung cancer and 154 050 lung cancer deaths (1). The two main types of lung cancer are small lung

carcinoma (SCLC) & non- small lung cancer (NSCLC) the latter is most common. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are a few of the other categories (sub-types) that included (2,43). The best treatment for Non-small-cell lung carcinoma (NSCLC) depends on the histopathologic subtype, next molecular features, and finally the tumor stage (3,44). Positron Emission Tomography – Computed Tomography with F 18 fluorodeoxyglucose (FDG) is recommended by the National Comprehensive Cancer Network (NCCN) for the assessment of patients who get lung cancer from stage I to stage IV Non-small-cell lung carcinoma (4,42). The usage of Fluorodeoxyglucose F18 (FDG) and Positron Emission Tomography – Computed Tomography (PET/CT) for staging in patients with Non-small-cell lung carcinoma (NSCLC) is recommended by the American College of Radiology Appropriateness Criteria, the Society of Nuclear Medicine and Molecular Imaging Guidelines, and the American College of Chest Physicians Guidelines .Radiologists and nuclear medicine physicians should be concerned about the usage of Fluorodeoxyglucose F18 and PET/CT in the modernization of categorization systems in order to offer precise staging info for improved treatment (5,6,41).

PATIENTS AND METHODS

Patients:

Prospective study was involved 100 patients (30 females and 70 male) with age rate from 36 to 90 years old (average 60 year). All patients were referred for Positron emission tomography–computed tomography PET-CT- scan which are proved by biopsy as NSCLC for initial staging with Fluorine-18 fluorodeoxyglucose–Positron Emission Tomography–Computed Tomography- SCAN, out of 100 patients 12 patients followed by another FDG –PET- CT- SCAN six months later after treatment to assess regression or progression of the tumor. Our patients were biopsied either by bronchoscope or CT guided Tru- cut biopsy in Al- Sader medical city in Al- Najaf – radiology department between February 2021- February 2022. The FDG PET –CT SCAN performed at Amir AL-Momineen specialty hospital oncology & nuclear medicine center. The report of FDG PET-CT scan done by a well experience specialist in nuclear medicine.

Methods:

The patients were examined in single center using single protocol and PET-CT machines (GE Discovery IQ 3rings PET CT system) using standard protocol, imaging from vertex to mid-thigh , caudocranially PET aquicision was acquired 2-3 minutes/bed post 65 minutes uptake time after injection (I.V) of fluorine-18 fluorodeoxyglucose, subsequently, with and without attenuation correction and the Q-clear algorithm, axial, coronal, and sagittal Positron emission tomography (PET) images were analyzed, and corresponding CT images without oral or IV contrast studies were conducted with an optima 540 16 slice CT, reassembled and merged with the Positron emission tomography (PET) images.

The CT images were on low dose protocol utilized for anatomical localization with Positron emission tomography (PET) images Fasting blood sugar was done for each patient at time of injection of the 18F-FDG.

Statistical analysis:

Data entered and analyzed using the statistical package for social sciences (SPSS) version 27. Data expressed as mean, standard deviation, frequencies and percentages according to the type of variable. Chi square test used to compare frequencies.

Comparison of mean SUV values at different sites was performed using Analysis of Variances (ANOVA) tests. Pairwise comparisons of SUV values of primary lesion, secondary lesion and Lymph node between each other was performed using multiple comparison Post-hoc tests

Comparison of mean SUV values according to staging was done by ANOVA. Receiver Operating Characteristic (ROC) curve used to assess the validity of PET scan in evaluation of staging of bronchogenic carcinoma. Level of significance set at 0.05, two tailed P. value as cutoff point below which the difference or correlation consider significant.

RESULTS

A total of 100 patients were enrolled in this study, out of them 76 from Al-Najaf province and 24 from other provinces, (Figure 1).

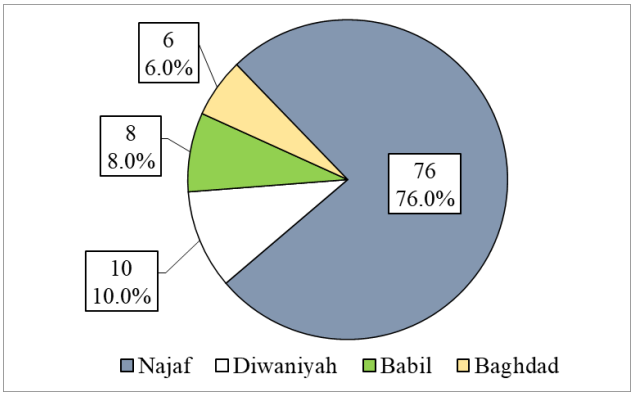

Figure 1. Distribution of the studied group according to address (N = 100).

Table 1 summarizes the socio-demographic characteristics of the studied group (100).

Variable		No.	%
Age (year)	≤ 40	13	13.0
	41 - 50	18	18.0
	51 - 60	21	21.0
	61 - 70	38	38.0
	> 70	10	10.0
	Median	60	-
	Range	36 - 90	-
Gender	Male	70	70.0
	Female	30	30.0
Occupation	Unemployed	45	45.0
	Employed	38	38.0
	Housewife	17	17.0
Smoking	Smoker	52	52.0
	Non-smoker	48	48.0
History of Hypertension	Yes	26	26.0
	No	74	74.0

Regarding the primary lesion, the median size was 3.30 x 3.12 x 3.01 cm and the largest lesion was 7.5 x 7.0 x 7.0 cm. For the secondary lesion it was 2.4 x 2.0 x 2.0 and the largest lesion dimension was 4.0 x 3.5 x 3.5, (Table 2).

Table 2. Size of Primary and secondary lesions of the studied group (N =100)

Lesion	Median Size (cm)	Largest lesion (cm)	Smallest lesion (cm)
Primary	3.30 x 3.12 x 3.01	7.5 x 7.0 x7.0	2.8 x 2.7 x 1.2
Secondary	2.4 x 2.0 x 2.0	4.0 x 3.5 x 3.5	1.4 x1.1 x1.0

The site of primary lesion of the studied group, left lower lobe was the more affected (27%) while right middle lobe was the least (1%). (table 3).

Table 3 site of primary tumors.

Position	No	%
• Left lower lobe	27	27.0
• Left upper lobe	23	23.0
• Right lower lobe	24	24.0
• Right upper lobe	14	14.0
• Right middle lobe	1	1.0
• Lingula	11	11.0
Outline		
• ill-defined	88	88.0
• Well-defined	12	12.0

The TNM staging of the primary lesions is demonstrated in (Table 4), more than 40% of cases with T1, N0 and M0. Moreover, T1(b/c) N0M0 reported in 47% of cases.

Table 4. demonstrates TNM staging.

TNM staging	**No.**	**%**
T		
T1b	5	5.0
T1c	51	51.0
T2a	18	18.0
T2b	10	10.0
T3	12	12.0
T4	4	4.0
Total	100	100.0
N		
N0	66	63.0
N1	16	15.0
N2	10	14.0
N3	8	8.0
Total	100	100.0
M		
M0	79	79.0
M1a	9	9.0
M1b	10	10.0
M1c	2	2.0
Total	100	100.0

Table 5. Combined TNM staging of primary lesions of the studied group.

TNM	Frequency	%
T1bN0M0	4	4.0
T1cN0M0	43	43.0
T1cN1M0	3	3.0
T2aN0M0	7	7.0
T2aN0M1a	2	2.0

T2aN1M0	2	2.0
T2bN0M0	2	2.0
T2bN0M1a	2	2.0
T2bN1M0	2	2.0
T3N0M0	4	4.0
T3N0M1a	2	2.0
T3N2M0	2	2.0
T4N1M0	2	2.0
Each of other TNM stages reported in only one patient: T1bN2M1b, T1bN3M1b, T1cN2M0, T1cN3M0, T1cN3M1a, T1cN3M1b, T2aN1M1b, T2aN1M1c, T2aN1Mb1, T2aN2M0, T2aN2M1a, T2aN2M1b, T2aN3M0, T2bN1M1b, T2bN1M1c, T2bN2M0, T2bN2M1a, T2bN3M0, T3N1M0, T3N1M1b, T3N3M1b, T4N2M0, T4N3M0		

Secondary lesions reported in 14 cases and were sited in liver (5 cases), MSK (4 cases), Supra renal gland (4 cases), and right kidney in only one case, (Table 6).

Table 6 Frequency distribution of sites of secondary lesions (N=14)

Site of secondary lesion	No.	%
Liver	5	35.7
MSK	4	28.6
Supra renal gland	4	28.6
Right kidney	1	7.1
Total	14	100.0

Pleural effusion and Lymphadenopathy (LAP) reported in 6 and 37 cases, respectively. The more frequent site of LAP was Left- hilar (10%), Right- hilar (8) followed by other sites.

The mean values of SUV of primary lesion, secondary lesions and lymph node are demonstrated in (Table 7). It had been significantly found that mean SUV of primary lesion was higher than that in secondary lesions and lymph nodes; 10.81, 9.71 and 9.62, respectively, (P. value < 0.05). Conversely, the SUV was not significantly different between secondary lesions and lymph node, (P. value >0.05).

Table 7 Comparison of mean SUV values at different sites

	Mean	Standard Deviation	P. value*
SUV primary lesion	10.81	2.42	0.008
SUV-secondary lesion	9.71	1.82	
SUV- Lymph node	9.62	1.34	
Multiple comparison (Post hoc) analysis			
SUV: Primary vs. Secondary			0.038
SUV: Primary vs. Lymph node			0.005
SUV: Secondary vs. Lymph node			0.676

Comparison of mean SUV values according to staging revealed significantly that SUV value increased with advancing stage, (Figures 2 & 3), (P. value <0.05).

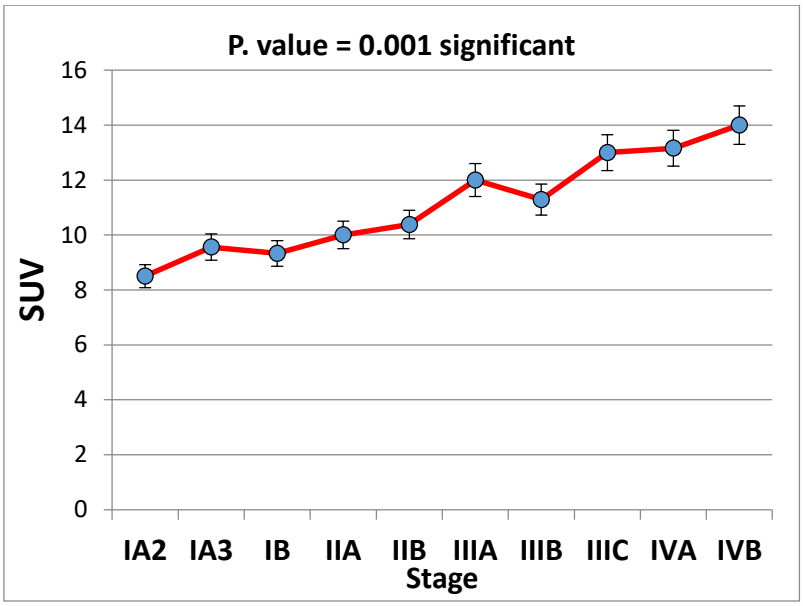

Figure 2 Line-marker plot showing the increase in SUV value with advancing stage grouping

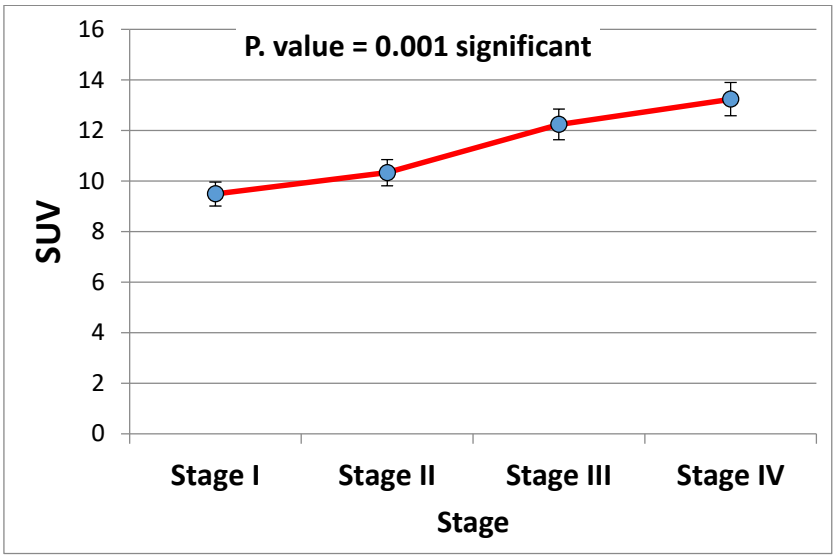

Figure 3. Line-marker plot showing the increase in SUV value with advancing stages.

Using receiver operating characteristic (ROC) curve for the analysis of validity of SUV to predict advanced stage (Figure 4), revealed that SUV was good predictor of advanced stage of malignancy, it produces an area under the curve of (0.906) at an optimal cutoff point of 10.5, above which giving a sensitivity, specificity and accuracy of 86.5%, 84.2% and 85.7%, respectively. The positive and negative predictive values were 84.5% and 86.2%, respectively.

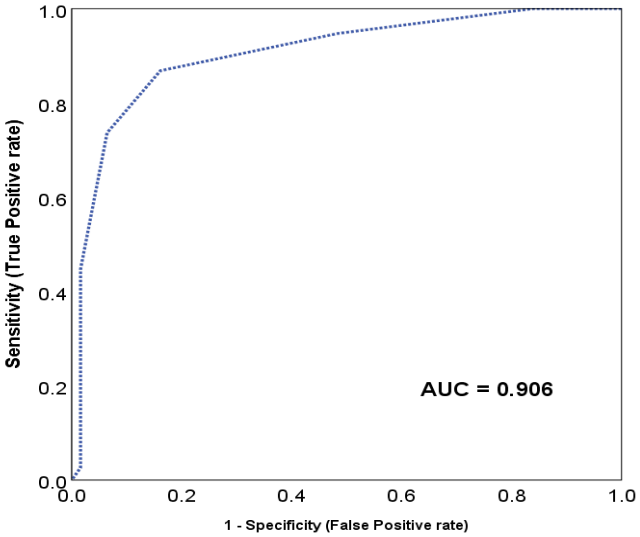

Figure 4. Receiver operating characteristic curve for the analysis of validity of SUV to predict advanced stage.

Only 12 patients were followed up and assessed. The mean initial SUV of primary lesion of the 12 patients was 10 ± 1.9 after follow up it was lowered to 8.3 ± 2.3, but the change did not reach the statistical significance, (P. value > 0.05). Similarly, the mean SUV of secondary lesions was 9.0 ± 0.9 initially and minimally changed to 8.7 ± 1.5 after follow Up with no statistically significant difference, (P. value > 0.05).

For the correlation between SUV of primary lesion before and after follow up, Spearman's correlation analysis revealed that initially a significant correlation between larger SUV value and advanced stage was found, (R = 0.623, P. value = 0.030). After follow up no such correlation was found, (R = 0.303, P. value = 0.338). No further statistical analysis can perform to assess the validity of SUV as predictor of advanced stage or prognosis after follow up due to small sample size, so the ROC analysis was not applicable.

Discussion

In Iraq, studies concerned with the evaluation of FDG-PET are almost unavailable, hence, the current study conducted to assess the role of PET CT in staging of disease and in follow up after treatment. To meet these aims, a total of 100 Iraqi patients were enrolled in the study with different stages of lung cancer. The demographic characteristics of the studied group revealed that only 24% of the cases are residents of other provinces other than Najaf, this is because the presence of Oncology center in our province with good facilities that could be not available in other neighboring provinces.

Present study showed a median age of 60 and more than two thirds of the patients were older than 50 years, on the other hand males were dominant contributed for 70% of the studied group and smokers were 52%. These findings were not unexpected because different epidemiological studies reported that incidence of lung cancer increased with advancing age, male gender and smokers, where smoking represents the top of list of the modifiable risk factors of lung cancer

As the age increases the incidence rate will dramatically increase for instance the incidence is 25/100000 in population younger than 20 years to reach 350/100000 population aged 45-49 years while the rate among those aged 60 years or older reach about 1000/100000, (7-9) that contributes the higher frequency of these factors among the studied group. The main complaints of the patients were shortness of breath, hemoptysis and cough were they contributed for 45%, 25% and 23%,

respectively, which is consistent with clinical picture of lung cancer that reported in earlier studies and literatures (10).

The current study showed that size of lesions varied among the patients, however, size of tumor depends on the time of diagnosis, stage of cancer and other factors. It is well known that lung cancer mainly diagnosed at more advanced stages and at larger size than other cancers did (11). Among the studied group, left lower lobe was the more affected, these findings agreed that reported in previous study, in Saudi Arabia, Alamoudi, reported that lower lobe affected in 27% of cases Alamoudi, 2010 (12), additionally other studies mentioned that lower lobe associated with poor prognosis Shien, *et al.* 2015(13).

In our study, 14% of cases had metastatic lesions, mainly to the liver, musculoskeletal and suprarenal gland, Milovanovic, *et al,*.2017 (14) documented that the most frequent metastasis occurs to liver and adrenal gland. Riihimäki, *et al.* 2014 (15) found that 35% of metastasis was to the liver, 39% to bones and 22% to respiratory system but 47% to nervous system.

In our study, the mean values of SUV of primary lesion was significantly higher than that secondary lesions and lymph nodes, in a study conducted by Dijkman*, et al,* 2010 (16), the SUV of primary tumor compared to metastatic tumor and other primary tumors, interestingly, Dijkman, *et al*. 2010(16) hypothesized that tumors which have similar clonal origin, are often shared histological features and the SUV of secondary tumors of clonally related primary tumors could be more similar, but they are not when compared to tumors with different clonal origin. Hence, they found no significant difference in SUV between primary and secondary tumors but they did when compared two primary tumors of different origin. Therefore, the significance difference found in our study could be attributed to this hypothesis and the secondary tumors were not of the same clonal origin.

Çalışkan ,*et al*. 2021 (17) studied 233 patients with lung cancer, results of their study revealed that SUV value of squamous cell carcinoma was significantly higher than that of adenocarcinoma and small cell carcinoma as primary tumor types, but they were insignificantly different across the stages of these three types of lung cancer, on the other hand, Çalışkan, et al. 2021 (17) concluded that SUV was not significantly different between nodal involvement of these carcinomas, and no significant difference with metastatic lesions.

Koksal, *et al*. 2013 (18) evaluated 334 mediastinal and hilar lymph nodes stations and found high SUV compared to the surrounding blood pool and the SUV ranged between almost 1.6 and 25, from other point of view, 14% of these lymph nodes were due to metastasis and these lymph nodes had a SUV of 2.5 or more. Koksal *et al*. 2013; (18) stated that different factors could affect the SUV, among these factors, glucose metabolism, types and number of tumor cells. The high SUV value could either be due to higher number of inflammatory cells, or high mitotic activity. Nonetheless, a large number of cells in a tumor is not necessarily associated with higher metabolic activity because it may a large number of cells in a tumor with low metabolic activity and vice versa Christensen, 2010 (19). Furthermore, Koksal, et al. 2013(18) documented that SUV of a tumor could be affected by the larger tumor size and necrosis. Which indicated a positive correlation between diameter of the tumor and SUV Koksal, et al. 2013 (18). These findings supported what was reported in earlier studies (20-22). It has been postulated that larger diameter of tumor was associated with more glucose transporter-1 expression, that results in increased FDG uptake.

The differentiation of primary lung cancer from metastatic one, is crucial in clinical practice, this is due to prognostic and therapeutic implication, where palliative treatment used in cases with metastatic lung cancer as it is incurable. From other point of view, patients with multiple primary cancers have almost similar survival rates compared to those with solitary primary lung cancer (16,23)

The current study found that the mean SUV value increased significantly with advancing stage. Similarly, Sahiner, et al. 2013(24) found that SUV value increases with advancing stage of lung cancer. The positive correlation between SUV value and stage of lung cancer may be due to volume effect where in small lesions, SUV can be lower than expected particularly in lesions less than 2.5 cm in size. In contrary, Çalışkan, *et al*. 2021 (17) found no significant differences in SUV value on PET/CT across the TNM stages. Furthermore, Kanzaki, *et al*.2010 (7) concluded that value of SUV of a primary tumor was significantly associated with larger diameter tumor and more advanced stage. It has been proved that tumors with larger size and diameters associated with more expression of glucose transporter 1, which in turn lead rise in FDG uptake Koksal*, et al*. 2013 (18).

Koksal, et al. 2013 (18) found that SUV of primary tumor was significantly higher in larger diameter tumors. On the other hand, Koksal, et al. 2013(18) found a significant correlation between pathological stage and tumor diameter and this reflected a positive correlation between the SUV of primary tumor and advanced stage of disease. Conversely, Çalışkan, et al. 2021(17). found no significant difference in SUV values between lung cancers with or without metastasis.

In the current study we found that SUV was good predictor of advanced stage of malignancy, it produces an area under the curve of (0.906) at an optimal cutoff point of 10.5, above which giving a sensitivity, specificity and accuracy of 86.5%, 84.2% and 85.7%, respectively. The positive and negative predictive values were 84.5% and 86.2%, respectively,

Previous studies, have mentioned that PET is more accurate than CT with a sensitivity of 79-85% and specificity of 87-92%, (25,26). Nonetheless, the false positive and false negative results of PET still under debate and need further assessment based on histopathology as gold standard.

In the present study only 12 patients were followed up and assessed, their age ranged between 39-74 years and their demographic characteristics were not much different than the main group. The duration since diagnosis ranged 3-12 months, 9 patients were smokers and 3 had history of hypertension. All the 12 patients had ill-defined outline lesions, non-cystic and non-calcified, 2 pulmonary depositions in left lung was reported, one patient with pleural effusion. Their primary lesion position was mainly in LLL and RUL, 50% of the 12 patients had LAP and only one metastasis to MSK while 2 patients had pulmonary deposit. The mean initial SUV of primary lesion of the 12 patients was relatively higher than that after follow up but the difference did not reach the statistical significance, (P. value > 0.05). Similarly, the mean SUV of secondary lesions after follow up was relatively lower than its initial value with no statistically significant difference, (P. value > 0.05). Regarding the correlation between SUV after follow up and staging, no significant correlation was found, this could be attributed either to small number of followed up patients or inability of SUV to predict the outcome and prognosis. However, we couldn't be sure about this finding because we couldn't have performed the appropriate statistical tests on the insufficient data so we couldn't demonstrate the validity of SUV as predictor or prognostic factor.

Conversely, Zhu, *et al*. 2017 (27) found that low SUV was strongly and significantly associated with overall survival of patients with non-small cell lung cancer after adjustment for age. Previous studies documented that PET/CT is an important diagnostic tool for staging of lung cancer, and useful in the transition to escalate the radiation doses. It had been postulated that failure of treatment in elective nodal stations is rare when chemo radiation guided by PET/CT Stephans, 2011(28).

Ibeas, et al. 2011(29) study showed that PET/CT scan able to provide prognostic information and can be used to monitor response to treatment and follow up of patients.

Rosenzweig, *et al*. 2004 (30) showed that 4 months' post-radiation, a better improvement was found in patients with PET SUV of < 3.5 compared to those with SUV>3.5 and the lower SUV value significantly associated with improved overall survival.

A systematic review included 13 studies and compared 1474 patients concluded that increased PET SUV was good prognostic variable for low overall survival Paesmans, *et al*. 2010 (31). This finding also confirmed by other two studies included patients with non-small cell lung cancer undergoing surgical resection and chemo-radiation for local advanced tumor (32,33).

Other two studies found no significant correlation between SUV and overall survival or prognosis (34, 35)

As a part of earlier study, Henderson*, et al*. 2010 (36), PET was repeated at 2, 26 and 52 weeks after therapy of 14 patients. Despite the SUV values decreased with the time but higher SUV value reported at 52 weeks of follow up where some patients still having SUV of > 3.5 and

Those patients died, indicated that persistent rising SUV is a poor prognostic point Henderson, *et al*. 2010 (36). Similarly, Vahdat, et al. 2010 (37) demonstrated a decrease in SUV value from 6.2 initially to 2.3 after follow up, and at 18-24 months the tumors had SUV values between 1.5-2.8. Authors, recommended further studies for more precise evaluation of the prognostic value of PET/CT.

Other studies, found that PET was an excellent predictor of metastasis as well as in evaluation of benign tumors Stphans, 2011 (28). Mac Manus, et al.2001 (38) concluded that PET was poor predictor of brain metastasis. Other studies found that PET is better in detection of bone metastasis and it was more accurate compared to bone scan (39,40). However, the value of PET SUV as prognostic evaluation still under debate and the question is still to be answered. In general, evidence established that high SUV values before treatment have poorer prognosis, but the exact mechanism for this is not well recognized Stphans, 2011 (28).

CONCLUSION

1. PET -CT –Scan appears to have important role and performance in evaluation and staging of bronchogenic carcinoma.

2. PET -CT –Scan demonstrated high performance in detection of mediastinal nodal and distant metastasis.

3. At cutoff value of SUV of 10.5, PET -CT –Scan produce high sensitivity specificity and accuracy of more than 85%.

4. Findings regarding the role of PET -CT –Scan in the follow-up and response to treatment was not enough and not precisely conclusive.

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