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ROLE OF ^{18}F-FDG PET/CT IN PREDICTING EGFR MUTATION AND POSITIVE ALK EXPRESSION IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER – A PROSPECTIVE STUDY

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ABSTRACT

Objective: Mutation in epidermal growth factor receptor (EGFR) and rearrangement of echinoderm microtubule associated protein-like 4 (EML4) –anaplastic lymphoma kinase (ALK) occurs in advanced non-small cell lung cancer (NSCLC) which can be successfully treated with tyrosine-kinase inhibitors. In some patients, biopsy is not feasible. We aimed to evaluate whether maximal standardized uptake value (SUVmax) of the primary tumor (pSUVmax), nodal metastasis (nSUVmax) and distant metastasis (mSUVmax) obtained from fluorine -18 fluorodeoxyglucose (^{18}F-FDG) PET/CT scan helps to non-invasively determine EGFR mutation and ALK rearrangement in NSCLC. **Material and Methods:** 65 patients with histopathologically confirmed NSCLC visiting our hospital from January 2021 to January 2023 underwent ^{18}F-FDG PET/CT scan prior to treatment. Their relevant clinicopathological data were obtained. pSUVmax, nSUVmax and mSUVmax were calculated and multivariate regression analysis has been applied to identify predictors of EGFR mutation and ALK rearrangement. **Results:** EGFR mutation and ALK rearrangement found in 29(45%) and 15(23%) patients respectively. Multivariate analysis revealed that low pSUVmax with cut-off of 8.65, high mSUVmax with cut-off of 9.2, female sex, adenocarcinoma and stage IV disease are better predictors of EGFR mutation. Similarly, high nSUVmax (cut off >4.4), male sex, non-smokers, adenocarcinoma and stage IV disease had higher association with ALK rearrangement. **Conclusion:** Our study concluded that low pSUVmax and high mSUVmax obtained from ^{18}F - FDG PET/CT scan when combined with relevant clinicopathological factors is a valuable tool for non- invasively predicting EGFR mutation. Similarly high nSUVmax obtained from ^{18}F - FDG PET/CT scan along with other relevant clinicopathological factors helps in predicting ALK rearrangement in patients whom biopsy cannot be obtained.

KEYWORDS

Epidermal growth factor receptor, Anaplastic lymphoma kinase, Mutation, Wild type, Rearrangement, Positron emission tomography, Fluorodeoxyglucose, Standardized uptake value

INTRODUCTION

Mutation in epidermal growth factor receptor (EGFR) and rearrangement of echinoderm microtubule associated protein-like 4 (EML4) –anaplastic lymphoma kinase (ALK) often leads to progression of disease in patients with advanced non-small cell lung cancer (NSCLC), especially in advanced adenocarcinoma (ADC). Tyrosine kinase inhibitors (TKIs) are effectively used to treat patients with mutation in the genes encoding EGFR and ALK. Thus, identifying EGFR mutation and positive ALK expression is of paramount importance before initiating targeted therapy against these genes in patients with non-small cell lung cancer [1].

Although tumor biopsy is the most commonly used method for detection of mutation of oncogenes, the biopsied site may not always demonstrate accurate result because of tumour heterogeneity. Also, the general condition of elderly patients may not permit biopsy.

To avoid these limitations, the use of a non-invasive molecular imaging modality using positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro–D-glucose integrated with computed tomography (^{18}F- FDG PET/CT) to predict the mutational status of EGFR and ALK in patients with NSCLC has been described in few studies [2].

FDG PET CT imaging is used for assessing glucose metabolism in tumors. The semi-quantitative parameter called Standardized uptake value (SUV) is used to measure FDG uptake in tumors. EGFR signalling impacts glucose metabolism in EGFR mutated lung cancer [3].

Previous studies have shown conflicting results between association of FDG uptake and EGFR mutational status and very few studies have shown correlation between ^{18}F-FDG avidity and ALK rearrangement. We have, therefore, carried out this study to evaluate whether ^{18}F-FDG PET/CT imaging can non- invasively predict EGFR mutation and ALK rearrangement (ALKr) in NSCLC. EGFR negativity is defined as EGFR wild - type in our study.

MATERIAL AND METHODS

Inclusion and exclusion criteria of patients

65 patients aged >18 years with biopsy proven cases of advanced NSCLC who visited the Medical Oncology outpatient department of our hospital from January 2021 to January 2023 are included in our study. All the patients underwent ^{18}F-FDG PET-CT scan. EGFR and ALK mutational status were analyzed. Patients whose time interval between sampling and PET-CT scan exceeded one month, patients with acute medical condition or having prior history of malignancy and patients who received treatment before undergoing PET-CT scan or before sampling for the gene alteration analysis were not included in our study. Age, sex, smoking history, histopathology, tumor size, lymph nodal involvement, distant metastasis is recorded. Non-smokers are defined as those who never smoked or smoked less than 100 cigarettes in their lifetime. Ex-smokers are defined as those who smoked more than 100 cigarettes in life time and quit smoking 1 year back. Tumor node metastasis (TNM) staging is based on AJCC 8th edition.

Acquisition and analysis of ^{18}F-FDG PET-CT scan

^{18}F-FDG PET-CT scan is performed on Siemens Biograph True Point PET/CT system. All patients fasted for atleast 6 hours before the scan. Blood glucose level of each patient confirmed to be less than 200mg/dl prior to injection of 3.7 -6.7 MBq/Kg of FDG. Scan acquisition conducted 1 hour after ^{18}F-FDG administration. Intravenous contrast is administered only if serum Creatinine level is less than 2mg/dl. A

region of interest (ROI) is placed over the primary tumor, nodal metastasis, and distant metastasis to measure each SUVmax (maximum Standardized Uptake Value). SUVmax calculated with the most commonly applied formula: SUVmax = maximum pixel activity / (injected dose /body weight).

EGFR mutation and ALK rearrangement analysis

EGFR mutation and ALK rearrangement is done by NGS (Next Generation Sequencing) method in our study to look for appropriate targeted therapy. Deletion in exon 19 and point mutation in exon 21 are most commonly encountered mutations in NSCLC. Dysregulated ALK kinase domain becomes active due to ALK rearrangement and resulting fusion protein formation. NGS testing has been preferred in our study as detailed mutational studies are possible and also commercial lung cancer specific fusion panel is available. Paraffin blocks have been used for DNA and mRNA extraction for NGS. High quality nucleic acids with proper QC are used to evaluate mutations or gene arrangements by sequencing method. Finally, data is collected for further comparison with FDG PET/CT scan

Statistical Analysis

Demographic patient data is analyzed using descriptive statistics. Data is expressed as mean ± SD. An Analysis of Variance (ANOVA) test is conducted to examine the relationship between categorical variables, such as age, sex, clinical stage, smoking status, and histopathological subtypes, in two groups. Statistical significance is determined at $p < 0.05$.

Receiver operating characteristic (ROC) curves are employed to assess the optimal cut-off values of PET/CT parameters (SUVmax) in predicting EGFR mutation and ALK rearrangement status. A significance level of $p < 0.05$ is used to evaluate statistical significance. Binary logistic regression analysis is performed to identify independent predictors of the EGFR and ALK rearrangement status. The predictive performance of the selected criteria is assessed by calculating the area under the ROC curve (AUC). All statistical analyses and graphs are generated using SPSS version 19.0 (IBM Corporation, Armonk, NY, USA) and Origin 8 (Origin Lab Corporation, USA) software.

Ethical Considerations

Ethical clearance has been obtained from the Institutional Ethics Committee before initiating the study (Ethical Committee Certificate No.SCI/ECR/2020/27). Informed consent is obtained from all patients. All patient data is kept confidential.

OBSERVATIONS AND RESULTS

Patient Characteristics

The study enrolled a total of 65 patients, with 29 (45%) testing positive for EGFR mutation (EGFR mutated) and 36 (55%) testing negative (EGFR wild type). Similarly, out of the 65 patients tested for ALK, 15 (23%) are positive for ALK, while 50 (77%) are negative (Table 1).

Among the patients, there are 37 men (57%) and 28 women (43%), with a median age of 54.5 years (range,31-82). Of the total, 43 patients (66.1%) are non-smokers. Histopathological analysis confirmed adenocarcinoma in 59 patients (91%), squamous cell carcinoma in 3 patients (4.6%) and other subtypes in 3 patients (4.6%). 15(23%) patients are classified as stage III while 50(77%) are classified as stage IV (Table 1).

The median maximum standardized uptake value of the primary tumor (pSUV max) is 10.8 (range, 1.7-23.6), that of lymph node (nSUV max) is 7.5 (range, 1.6-22), while that of distant metastasis (mSUV max) is 6.1 (range, 2.3-20) (Table 1).

Association between clinical characteristics with EGFR, ALK mutations

EGFR mutation is more frequently observed in women (59%, $p< 0.001$) compared to men (41%), non- smokers (75.86%, $p< 0.001$), patients with adenocarcinoma (96.5%, $p< 0.001$), and stage IV patients (79.31%, $p<0.001$) (Table1, Figure1).

ALK rearrangement is found more commonly in males (73%, $p<0.001$) compared to females (27%), non-smokers (53.33%, $p<0.001$), patients with adenocarcinoma (100%, $p<0.001$), and stage IV patients (73.33%, $p<0.001$) (Table 1, Figure 2).

Association between PET/CT Parameters with EGFR and ALK status

The mean maximum standardized uptake value of the primary tumor (pSUVmax), lymph node (nSUVmax), and distant metastasis (mSUVmax) in EGFR-mutated patients is 9.61±5.16, 5.85±4.47 and 6.42±7.1 respectively. In patients with EGFR-wild type, the corresponding values are11.69±5.43, 8.59±6 and 5.89±5.52 respectively. Notably, mSUVmax is the only PET parameter that showed a higher value in EGFR-mutated patients compared to EGFR-wild type patients. Significant statistical differences are found between EGFR-positive and EGFR-negative patients in terms of tumor stage, pSUVmax, and mSUVmax ($p < 0.001$) (Table 1).

The mean pSUVmax, nSUVmax, and mSUVmax in ALK-positive patients is 9.9±5.49, 8.35±4.6 and 5.76±4.13 respectively, while in ALK-negative patients, the values are 11.02±5.43, 7.22±5.73 and 6.21±6.76 respectively. Notably, nSUVmax is the only PET parameter that exhibited a higher value in ALK-positive patients compared to ALK-negative patients. Significant statistical differences are found between ALK-positive and ALK-negative patients in terms of tumor stage, nSUVmax, ($p < 0.001$) (Table 1).

Prediction of the EGFR and ALK mutation status

Our study is conducted across 65 patients to evaluate the diagnostic effectiveness of ^{18}F-FDG PET/CT scan in predicting EGFR mutation and ALK status in advanced NSCLC patients.

The binary logistic regression analysis showed that sex, smoking status, histology, tumor stage, pSUVmax, nSUVmax, and mSUVmax are statistically significant variates that are associated with EGFR mutation and ALK rearrangement status. The inclusion of these factors together in the multivariate regression analysis revealed that sex, smoking status, histology, tumor stage, pSUVmax, nSUVmax, and mSUVmax remained independent variables for predicting EGFR mutation and ALK rearrangement status.

Subsequently, ROC curve analyses have been performed through which the cutoff value of pSUVmax for predicting EGFR mutation has been found to be 8.65, with Area under Curve (AUC) 0.374, sensitivity,48.3%, specificity, 25%, CI, 95%. P value is not significant since AUC is less than 0.50. However, incorporating a combined variable including sex, age, smoking history, histological type, stage along with pSUVmax provided better predictive capability for EGFR mutation status with AUC, 0.711, sensitivity,72.4%, specificity, 69.4%, CI, 95% and p value of 0.01.(Figure 3a and 3b). The nSUVmax is not associated with EGFR mutational status in our study (Figure 4).

EGFR mutated patients showed higher value of mSUVmax in our study compared to patients with EGFR wild-type with cutoff point of 9.2 and AUC, 0.504. However, the AUC value increased to 0.71 on combining mSUVmax with other clinicopathological factors (Figure 5a and 5b).

The cutoff point of nSUVmax in our study for predicting ALK rearrangement is 4.45 with AUC, 0.595, sensitivity,86.7%, specificity, 40%, CI 95% and p value of 0.05. The AUC value increased to 0.843 on combining nSUVmax with other clinicopathological factors (Figure 6a and 6b). The pSUVmax and mSUVmax are not associated with the ALK status (Figure 7,8). PET/CT images of patients with EGFR mutant, wild-type and ALK rearrangement are shown in Figures 9-11.

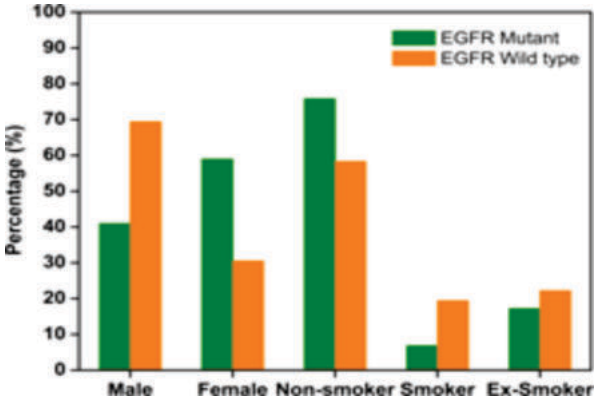

Figure 1: The graph showing the occurrence of EGFR mutation in different smoking status and sex of the patients.

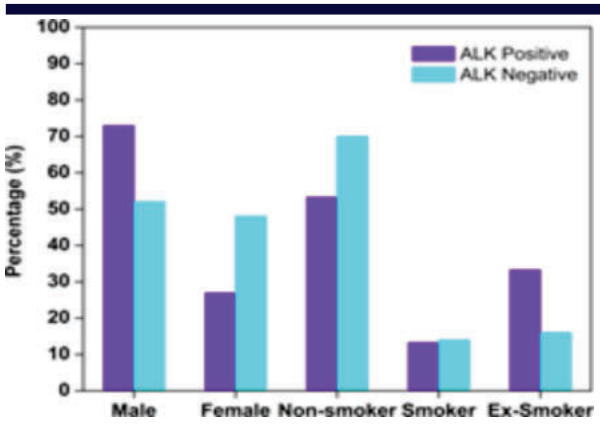

Figure 2: The graph showing the occurrence of ALK rearrangement status in different smoking status and sex of the patients.

Table 1: Association between ^{18}F-FDG PET/CT radiometabolic markers and EGFR mutation, ALK expression in NSCLC

Characteristics	EGFR Mutant	EGFR Wild type	p value	ALK Positive	ALK Negative	p value
Age (years), Mean ± SD (range)	54.96 ± 10.32 years (Range: 31-81)	54.05±11.64 Years (Range: 33-82)	p<0.001	48.47± 10.91 years. (Range: 33-69)	56.26±10.47 Years. (Range: 31-82)	p <0.001
Sex			p<0.001			p<0.001
Male	12 (41%)	25 (69.44%)		11 (73%)	26 (52%)	
Female	17 (59%)	11 (30.56%)		4 (27%)	24 (48%)	
Smoking status			p<0.001			p<0.05
Nonsmoker	22 (75.86%)	21 (58.33%)		8 (53.33%)	35 (70%)	
Smoker	2 (6.89%)	7 (19.44%)		2 (13.33%)	7 (14%)	
Ex-Smoker	5 (17.24%)	8 (22.22%)		5 (33.33%)	8 (16%)	
Stage			p<0.001			p<0.001
I	0	0		0	0	
II	0	0		0	0	
III	6 (21%)	9 (25%)		4 (26.67%)	11 (22%)	
IV	23 (79.31%)	27 (75%)		11 (73.33%)	39 (78%)	
Tumour size in PET/CT	4.4±3.4 x 3.7±2.8	4.4±3.2 x 4.1±2.5	p<0.001	3.4±2.1 x 3.3±1.8	4.7±3.5X 4.1±2.8	p<0.001
pSUV max (Mean ± SD)	9.6 ± 5.16	11.69 ± 5.43	p<0.001	9.9±5.49	11.02±5.43	p<0.001
nSUV max (Mean ± SD)	5.85±4.47	8.59±6	p<0.001	8.35±4.59	7.22±5.73	p<0.001
mSUV max (Mean ± SD)	6.42±7.09	5.89±5.52	p<0.001	5.76±4.13	6.21±6.76	p<0.001
Histology			p<0.001			p<0.001
Adeno-carcinoma	28 (96.5%)	31 (86.1%)		15 (100%)	44 (88%)	
Squamous Cell Carcinoma	0	3 (8.3%)		0	3 (6%)	
Others	1 (3.5%)	2 (5.6%)		0	3 (6%)	

EGFR-pSUVmax
Area Under the Curve:0.374
Range: 0.512-0.235
Sensitivity: 0.483
1 – Specificity: 0.75
Specificity: 0.25
CI: 95%
Cut off: 8.65

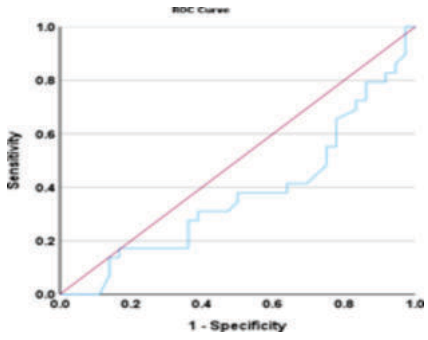

Figure 3a: Receiver operating characteristic curve of primary tumor SUVmax (pSUVmax) for predicting EGFR mutation

EGFR-pSUVmax with independent variables
Area Under the Curve: 0.711
Range: 0.838-0.583
Sensitivity: 0.724
1 – Specificity: 0.306
Specificity: 0.694
CI: 95%
Cut off: 0.41, p value:0.01

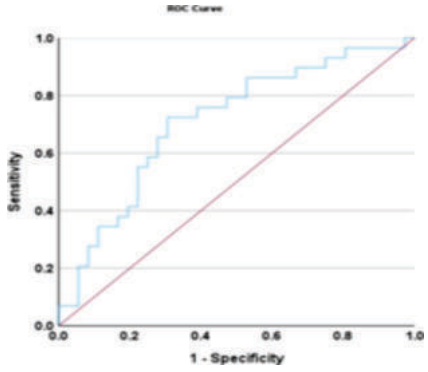

Figure 3b: Receiver operating characteristic curve of primary tumor SUVmax(pSUVmax) and combination of other factors (pSUVmax, sex, age, smoking history, histological type, stage,) for predicting EGFR mutation

EGFR-nSUVmax
Area Under the Curve: 0.378
Range: 0.514-0.242
Sensitivity: 0.103
1 – Specificity: 0.33
Cut off: 10.7

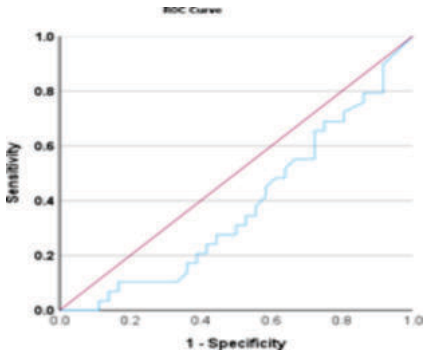

Figure 4: Receiver operating characteristic curve of lymph node SUVmax(nSUVmax) for predicting EGFR mutation

EGFR-mSUVmax
Area Under the Curve: 0.504
Range: 0.651-0.358
Sensitivity: 0.379
1 – Specificity: 0.25
Specificity:0.75
CI: 95%
P value: 0.05
Cut off: 9.2

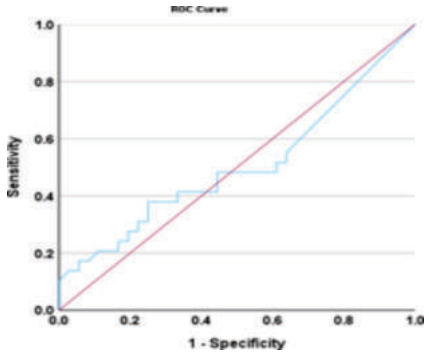

Figure 5a: Receiver operating characteristic curve of distant metastasis SUVmax (mSUVmax) for predicting EGFR mutation

EGFR-mSUVmax with independent variables
Area Under the Curve: 0.71
Range: 0.841-0.579
Sensitivity: 0.621
1 – Specificity: 0.222
Specificity: 0.778
CI:95%
P value: 0.01
Cut off: 0.54

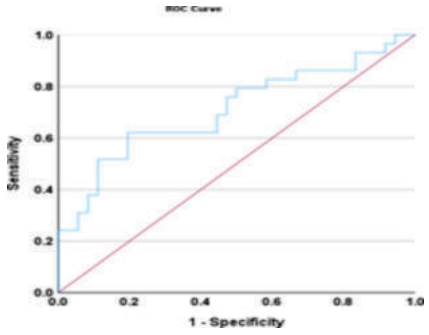

Figure 5b: Receiver operating characteristic curve of distant metastasis SUVmax (mSUVmax) and combination of other factors (mSUVmax, sex, age, smoking history, histological type, stage) for predicting EGFR mutation

ALK-nSUVmax
Area Under the Curve: 0.595
Range: 0.740-0.450
Sensitivity: 0.867
1 – Specificity: 0.6
Specificity:0.40
CI:95%
P Value:0.05
Cut off: 4.45

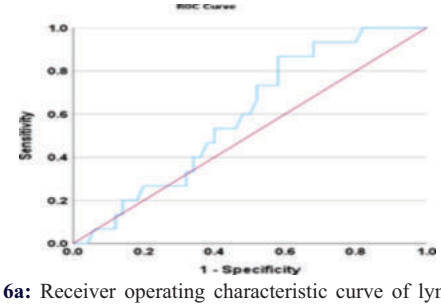

Figure 6a: Receiver operating characteristic curve of lymph node SUVmax (nSUVmax) for predicting ALK rearrangement.

ALK-nSUVmax with independent variables
Area Under the Curve: 0.843
Range: 0.946-0.74
Sensitivity: 0.8
1 – Specificity: 0.18
Specificity: 0.82
CI:95%
P value: 0.001
Cut off: 0.28

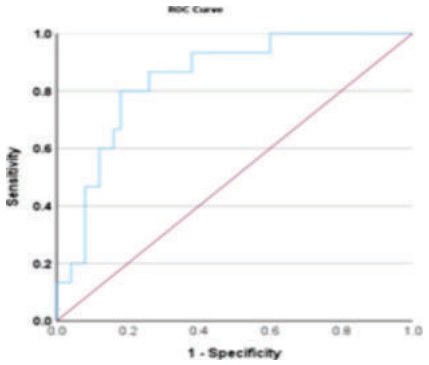

Figure 6b: Receiver operating characteristic curve of lymph node SUVmax (nSUVmax) and combination of other factors (nSUV max, sex, age, smoking history, histological type, stage) for predicting ALK rearrangement

ALK-pSUVmax
Area Under the Curve: 0.440
Range: 0.608-0.272
Sensitivity: 0.2
1 – Specificity: 0.4
Cut off: 11.15

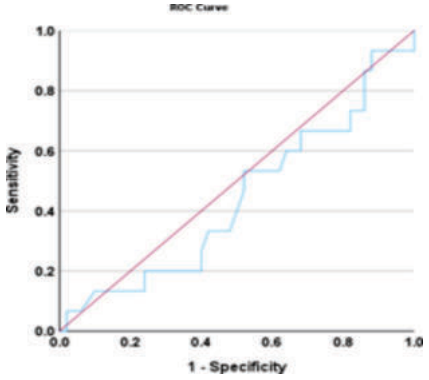

Figure 7: Receiver operating characteristic curve of primary tumor SUVmax (pSUVmax) for predicting ALK rearrangement

ALK-mSUVmax
Area Under the Curve: 0.509
Range: 0.655-0.362
Sensitivity: 0.733
1 – Specificity: 0.5
Cut off: 4.75

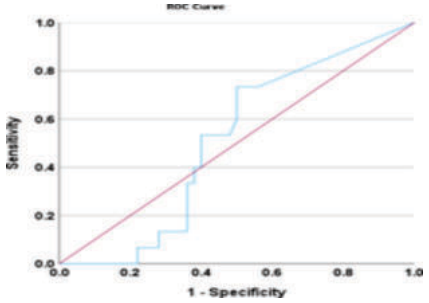

Figure 8: Receiver operating characteristic curve of distant metastasis SUVmax (mSUVmax) for predicting ALK rearrangement

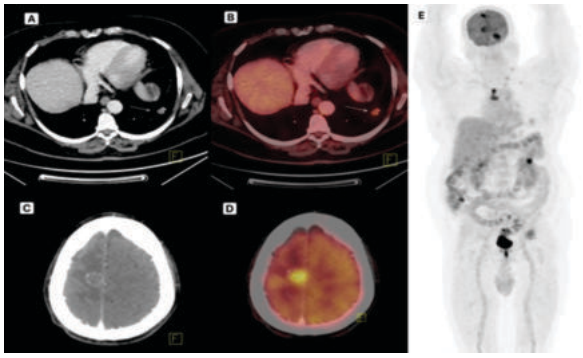

Figure 9: 55-year-old man with EGFR mutated stage IV lung Adenocarcinoma. CT and PET images show a 2.0 x1.6 cm lesion in lower lobe of left lung (A, B) with pSUVmax = 5.6, metastatic lesion in brain (C, D) with high mSUVmax =19.3. E is MIP image

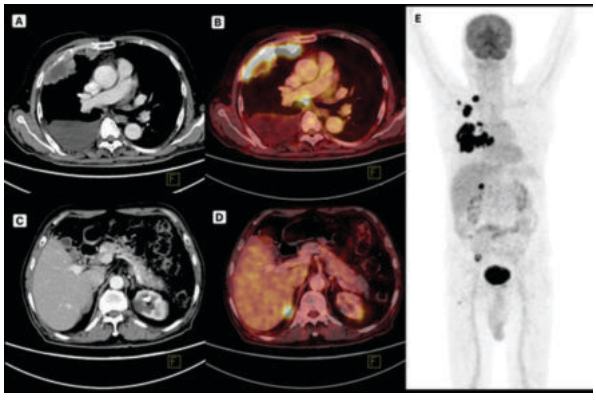

Figure 10: 82-year-old man with EGFR- wild type stage IV lung Adenocarcinoma. CT and PET images show a 6.0 x 3.4 cm lesion in right middle lobe (A, B) with high pSUVmax = 21. Patient also has metastasis in right adrenal (C, D) and in right ilium visible in MIP image(E).

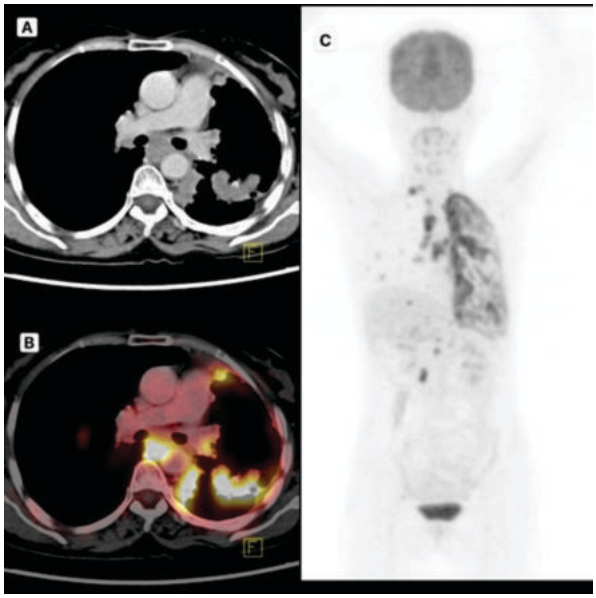

Figure 11: 48-year-old female with ALK rearranged stage IV lung Adenocarcinoma. CT and PET images show a 3.3 x 3.5 cm lesion in left lower lobe (A, B) with pSUVmax = 9.2 and mediastinal nodes with nSUVmax = 10.9.

DISCUSSION

In our study, we found higher frequency of EGFR mutation in women and non-smokers which is consistent with various other studies [4-8]. However, Jianxiong Gao et al reported higher frequency of EGFR mutation in males and in patients with positive smoking history [9]. Patients with Adenocarcinoma has higher frequency of EGFR mutation in our study which is concordant with other studies [10,11]. However, histopathology of majority of the patients in our study consisted of Adenocarcinoma. We had only fewer patients with histopathology other than Adenocarcinoma.

In the study of Zhilei LV et al, EGFR mutation is more frequent in stage I patients even though the study had higher number of stage IV patients compared with stage I disease (56.8% Vs 17.5%) [12]. According to few studies, EGFR mutational status is not significantly affected by tumor stage [13,14]. In our study, higher frequency of EGFR mutation has been observed in patients with stage IV disease, however our study included only those patients having stage III and stage IV disease. Patients with stage I and stage II disease are not included in our study.

In our study, lower value of pSUVmax (cutoff of 8.65) has been found in EGFR mutated patients compared to patients with EGFR wild type. The sensitivity and specificity of determining EGFR mutational status however increased on combining pSUVmax with other clinicopathological factors as described above. Our cutoff value of PSUVmax is almost similar with that of many other studies. Na et al reported cutoff of 9.2 (AUC value 0.74, sensitivity,72%, specificity: 67%), Zhilei LV et al has reported cutoff of 7.0 (AUC value 0.557, sensitivity,72.8%, specificity,38.5%) and Cho et al has reported cutoff of 9.6 with AUC value 0.68, sensitivity,79.3% in EGFR mutated patients [10,12,15]. Also, in the study of Zhu et al, patients with EGFR mutation had lower SUVmax (7.70) than the patients with EGFR wild type [16]. Many other studies have reported lower value of pSUVmax in EGFR mutated patients compared to EGFR wild type [9,17]. However, Wang et al has reported higher value of pSUVmax (cutoff >10.92) in EGFR mutated patients compared to EGFR wild type [18]. Huang et al [19] and Ko et al [20] have also reported higher value of pSUVmax in EGFR mutant than wild type in their studies. However, their results were not statistically significant.

Literature on nSUVmax for predicting EGFR mutational status in lung Adenocarcinoma is very scanty. In our study also, the AUC value of nSUVmax for predicting EGFR mutational status is only 0.37.

Our study found higher value of mSUVmax in EGFR-mutated patients compared to EGFR-wild type (cutoff of 9.2) with AUC 0.504. However, the AUC value increased to 0.71 on combining mSUVmax with other clinicopathological factors. Our finding is almost similar with that of Wang et al where cutoff of SUVmax obtained from metastatic lesions in EGFR mutated patients is >10.6 [18]. More studies are required to validate this finding.

In the study of Gayaf et al and Jiang et al, there were no significant differences between nSUVmax, mSUVmax and EGFR mutation [11,17].

ALK rearrangement has been found to be more common in non-smokers and in patients with Adenocarcinoma of Stage IV disease in our study which is also documented in other studies [11,21,22]. Males had higher frequency of ALK rearrangement in our study compared to females which is concordant with the finding of Gayaf et al [11]. However, Choi et al has reported more females than males in ALK rearranged patients [22].

In our study, nSUVmax exhibited a higher value in ALK- rearranged patients (ALKr) compared to ALK- wild type patients with the cutoff value of 4.45 and AUC value 0.595. The AUC value further increased on combining nSUVmax with other clinicopathological factors. Our study result is concordant with that of Lv et al [12]. However, in this study cutoff value of nSUVmax has not been mentioned and also no significant relationship has been found between pSUVmax and ALKr. The pSUVmax and mSUVmax is not associated with the ALK status in our study. According to Jeong et al, higher pSUVmax is an independent predictor of ALK rearrangement [21]. Ruan et al observed significantly higher pSUVmax (12.56±7.06) in patients with ALKr compared to the ALK wild type group in patients with lung Adenocarcinoma. However, the study did not find such significance in nSUVmax [23].

Gayaf et al reported no significant difference in pSUVmax, nSUVmax and mSUVmax values between ALK positive and ALK negative groups in NSCLC [11]. In the study of Igde et al, SUVmax could not be validated to predict EGFRm or ALKr in lung Adenocarcinoma [24].

Such varied results among different studies are because of factors like

tumor heterogeneity, different studies including patients with different stages of disease as well as tumors with different sizes, different histopathology. Also, different centers may have slightly different protocols in acquiring FDG PET/CT scan.

CONCLUSION

Our study concluded that pSUVmax < 8.65 and mSUVmax > 9.2 along with other clinicopathological factors is predictive of EGFR mutation in advanced NSCLC. Similarly, nSUVmax > 4.45 along with other clinicopathological factors is predictive of ALK rearrangement in NSCLC. However, further prospective studies with larger sample size are required to determine the value of cutoff point of pSUVmax, nSUVmax and mSUVmax in evaluation of EGFR mutational status and ALK rearrangement in patients with advanced NSCLC. Probably our study is the only one which is providing cutoff values of mSUVmax in EGFR mutation and nSUVmax in ALK rearrangement as we could not find other relevant studies in literature providing these values

Limitations of the study

The study has relatively small sample size. Data is collected from a single centre; hence the patient population is not big enough. Also, since ALK rearrangement occurs in only 5% of patients with NSCLC, we had only fewer number of patients in the ALK rearranged group which is an unavoidable limitation.

Conflict of interest: The authors declare that they have no conflict of interest

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