National Board of Examination - Journal of Medical Sciences

Volume 1, Issue 4, Pages 188–197, April 2023

DOI 10.61770/NBEJMS.2023.v01.i04.002

ORIGINAL ARTICLE

F-18 FDG PET/CT characterization and predictive efficacy for driver mutation positive and negative pulmonary adenocarcinoma in correlation with clinico-pathologic data

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Accepted: 19-March-2023 / Published Online: 01-April-2023

Abstract:

Background: Fluorine-18 (isotope)-Fluoro-deoxyglucose positron emission tomography computed tomography (F-18-FDG PET/CT) as a non-invasive method could predict driver mutation status in pulmonary adenocarcinoma.

Aim: To assess whether F-18 FDG PET/CT can differentiate between positive and negative driver mutation status of pulmonary adenocarcinoma.

Settings and Design: Hundred biopsy proven, untreated pulmonary adenocarcinoma patients tested for EGFR and ALK gene mutations underwent staging F-18 FDG PET/CT scan at our institute.

Methods and Material: Metabolic parameters like SUV_{max} of the primary ($pSUV_{max}$), SUL_{peak}, SUV_{mean}, Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) of primary lesion, SUV_{max} of the most avid metastatic regional lymph node ($nSUV_{max}$) and extra thoracic metastasis ($mSUV_{max}$) and average SUV_{max} of the primary lesion, regional nodal metastasis and extra thoracic metastasis were calculated.

Statistical Analysis Used: The independent sample 'T' test and Mann-Whitney U test were used for analysis. Receiver operating characteristic (ROC) curves were used to determine the cut-off value of $pSUV_{max}$ for predicting ALK mutation status.

Results: Fourty one patients showed EGFR mutations, 14 showed ALK rearrangements and 45 were wild-type. Patients with ALK rearrangements showed a lower $pSUV_{max}$, SUL_{peak}, SUV_{mean} and TLG compared to wild type patients. ROC curve analysis showed a $pSUV_{max}$ cutoff of $\leq$11.0 yielding an area under the curve (AUC) of 0.709. Patients with EGFR mutations showed a lower $mSUV_{max}$, MTV, and TLG compared to wild type.

Conclusions: FDG- PET/CT can be a useful non- invasive tool if tumor tissue is not available, although genetic testing continues to be the gold standard.

Keywords: FDG/PET CT, driver mutation, pulmonary adenocarcinoma, metabolic parameters, EGFR, ALK.

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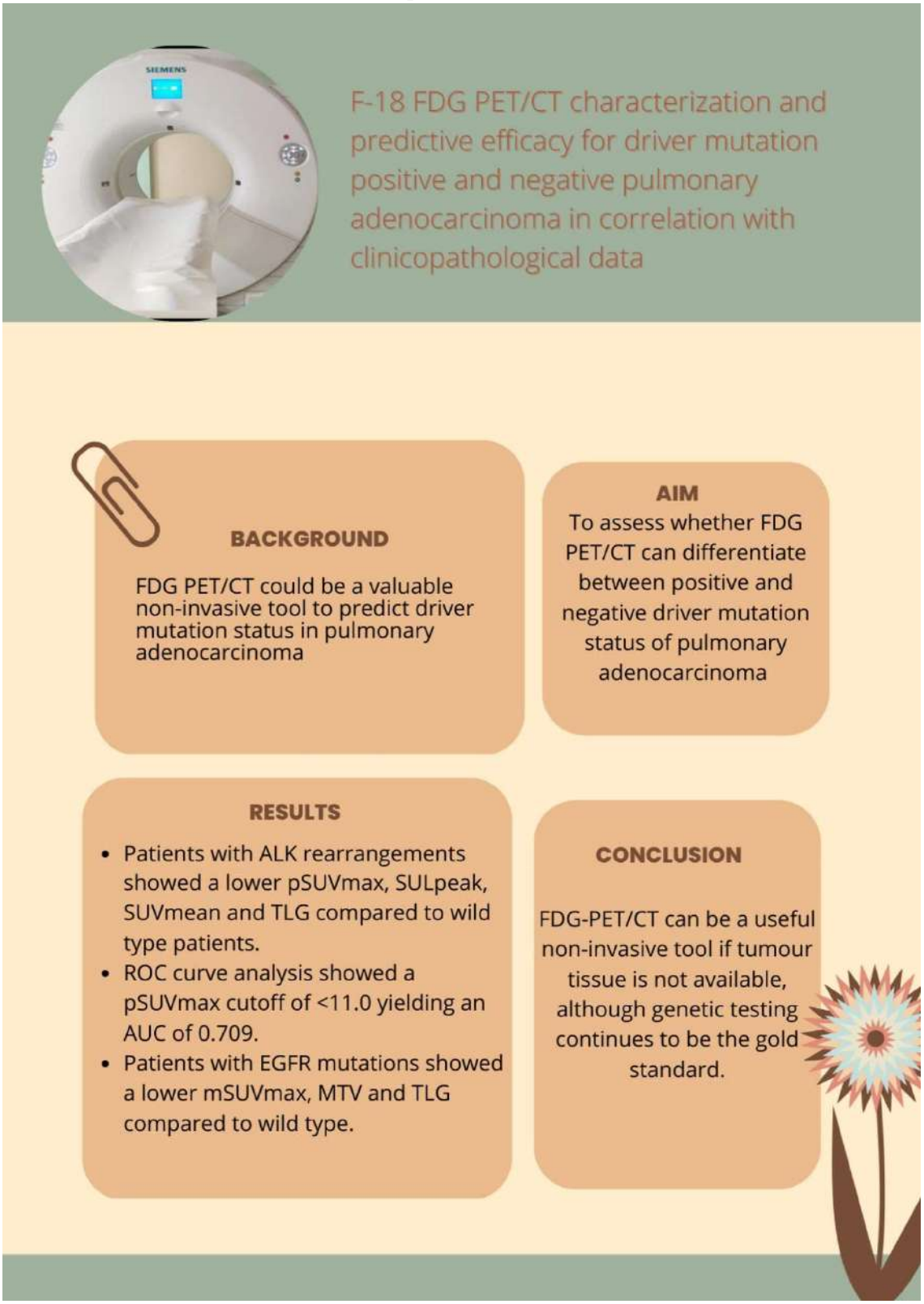
Graphical Abstract



Introduction

The discovery of mutations in lung cancer has resulted in the creation of targeted therapies which help in improving the survival of patients with metastatic cancer. Specific mutations in genes encoding components of the epidermal growth factor receptor (EGFR) and downstream mitogen-activated protein kinases (MAPK) and phosphatidylinositol 3-kinases (PI3K) signaling pathways can now be used to designate subsets of adenocarcinoma. This can be exploited by targeted therapies. Targeted EGFR treatments, for example, have enhanced response rates in patients with EGFR mutations when compared to standard chemotherapies. Tyrosine kinase inhibitors (TKIs), including gefitinib and erlotinib, were developed and have demonstrated to be an excellent treatment for individuals with EGFR gene mutations [1]. Fusion of ALK with EML4 genes forms translocation products that are responsive to pharmacological inhibition of ALK by agents such as crizotinib. Therefore, it is essential to identify EGFR and ALK mutation status before attempts at targeted therapy.

Fluorine-18(isotope)–Fluoro-deoxygl-ucose positron emission tomography computed tomography (F-18-FDG PET/CT) is a valuable modality which combines the metabolic and anatomic information in assessing the lesion. Tumor biopsies for the detection of oncogenic driver mutations have limitations. The site of tumor biopsy may have a significant impact on the detection and outcome, and the patients' overall health may limit the use of biopsies in clinical practice. Therefore, the use of medical imaging as a non-invasive method to obtain information about the tumor phenotype could provide clues to predict mutation status of the EGFR and ALK gene. This has been investigated in several studies wherein F-18-FDG PET/CT has been used to predict the mutation status of EGFR and ALK in patients with lung adenocarcinoma. However, the results remain controversial [2].

The goals of this study were to see if metabolic parameters from F-18-FDG PET/CT and clinicopathological data could predict EGFR and ALK expression and mutation status in patients with lung adenocarcinoma, and to create a prognostic template based on changes in EGFR/ALK mutation status, which can be used to guide individualized molecular targeted therapy.

Methods

This prospective observational study was conducted from December 2020 to February 2022 in our institute after approval from the Institutional Ethics Committee. It consisted of hundred patients with inclusion criteria being patients with biopsy proven pulmonary adenocarcinoma in whom EGFR and ALK mutation analysis was performed and the patient not started on any treatment before the scan. The exclusion criteria included patients who underwent previous treatment with chemotherapy/radiotherapy or surgery before scan, and patients with pulmonary adenocarcinoma in whom driver mutation analysis was not done.

Patients were subjected to the F-18 FDG PET/CT scan after obtaining prior informed consent. Patients were instructed to come fasting for atleast 6 hours. Blood sugar levels, height, weight, blood urea, and creatinine of the patient were recorded. A single injection of 5-10 mCi of F-18 FDG was injected intravenously through a secured I.V line as per standard protocol, based on the patient's weight. Whole-body F-18 FDG-PET/CT scan was performed at 60 minutes post-injection on Siemens Biograph mCT PET/CT scanner with 40 slice CT (diagnostic contrast-enhanced CT)(CECT).

The matrix used was 128 x128 for PET & 512 x512 for CT. Image reconstruction was done with OSEM (ordered subset expectation maximization), iterative reconstruction method. CT scan was then fused with PET images and transferred to the processing system for analysis.

PET/CT images were analyzed on a dedicated workstation that was provided with commercial software called Syngo. via. A large region of interest (ROI) involving the entire

primary tumor was drawn for the calculation of the metabolic parameters which were calculated by the syngo.via software (Figure 1). The maximum standardized uptake value (SUV_{max}) was calculated as the activity in the hottest voxel of the tumor. Maximum standardized uptake value corrected for lean body mass (SUL_{peak}) algorithm automatically identified the mean value of the voxels within a fixed sphere of $1cm^3$, centered on the hottest area of the tumor.The global semiquantitative parameters like mean standardized uptake value (SUV_{mean}), metabolic tumor volume (MTV) and tumor lesion glycolysis (TLG) were automatically calculated by the software based on the fixed relative threshold method with threshold fixed to 40 %, i.e., the lesion limits were determined by selecting all voxels within 40% of the SUV_{max} inside the master voxel of interest (VOI) drawn around the lesion.

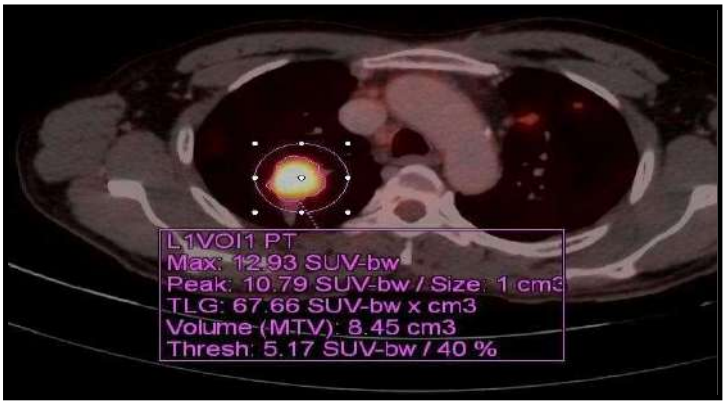


Figure 1. Selection of ROI for analysis of FDG-PET parameters

SUV_{max} of the most avid metastatic regional node ($nSUV_{max}$) if present was calculated. SUV_{max} of the most avid extrathoracic metastasis ($mSUV_{max}$) if present was calculated. Average SUV_{max} of the primary lesion ($pSUV_{max}$), regional nodal metastasis ($nSUV_{max}$) and extrathoracic metastasis ($mSUV_{max}$) was calculated using the formula

$$\text{Average } SUV_{max} = \frac{pSUV_{max}+nSUV_{max}+ mSUV_{max}}{3}$$

Statistical Analysis

All continuous variables were represented by mean ± standard deviation. Percentages were used to represent all categorical variables. The independent sample' T' test was used to compare continuous variables that were normally distributed. The Mann-Whitney U test was used to compare continuous variables that were not regularly distributed. Receiver operating characteristic (ROC) curves were used to determine the cut-off value of the primary tumor SUV_{max} ($pSUV_{max}$) for predicting ALK mutation status. Data was entered into a Microsoft Excel spreadsheet. SPSS (Statistical Package for Social Sciences) version 26.0 was used to analyze the data. P values less than 0.05 were deemed statistically significant.

Results

This study included 100 patients, 29 of whom were female (29 percent) and 71 of them were male (71 percent). Patients ranged in age from 28 to 85 years old. The bulk of the participants were between the ages of 51 and 70, with the median age being 57 years.

Ten patients were histopathologically well differentiated, i.e. Grade I (10%), 64 were moderately differentiated, i.e. Grade II (64%), and 26 were poorly differentiated, i.e. Grade III (26%).

Patients were staged according to AJCC 8th edition of TNM in lung cancer which is the standard of NSCLC staging since January 1st, 2017 [3]. Five patients belonged to stage I (5%), 1 belonged to stage II (1%), 18 belonged to stage III (18%), and 76 belonged to stage IV (76%).

Among the 100 patients who were tested for EGFR and ALK mutations, 41 were positive for EGFR mutation (41%). 14 showed ALK rearrangement (14%) and remaining 45 were wild type (45%).

Amongst the 41 patients who showed EGFR mutation, 8 were female (19.5 %) and 33 female (80.5%). 34 patients were well to moderately differentiated (82.9 %) whereas 7 patients were poorly differentiated (17.1 %). 3 patients belonged to stage I- II (7.3 %) while 38 patients were of stage III-IV (92.7 %).

Out of the 14 patients who showed ALK rearrangement, 7 were female (50 %) and 7 were male (50 %). 6 patients were well to moderately differentiated (42.9%) whereas 8 patients were poorly differentiated (57.1%). 1 patient belonged to stage I-II (7.1 %) while 13 patients were of stage III-IV (92.9 %).

Amongst the 45 patients who were EGFR and ALK wild type, 14 were female (31.1%) and 31 were male (68.9%). 34 patients were well to moderately differentiated (75.6%) whereas 11 patients were poorly differentiated (24.4%). 2 patients belonged to stage I-II (4.4%) while 43 patients were of stage III-IV (95.6%).

Metabolic Parameters

pSUVmax was lower in ALK positive patients (7.3 ± 4.2) compared to EGFR positive (11.1 ± 5.6) (p = 0.024) and wild type patients (11.8 ± 5.5) (p =0.007), both of which were statistically significant. pSUVmax was lower in EGFR positive patients (11.1 ± 5.6) compared to wild type patients (11.8 ± 5.5). However, the difference was not found to be statistically significant (p = 0.589).

To determine the cut-off value of the pSUVmax for predicting ALK mutation status, receiver operating characteristic (ROC) curves were plotted. The ROC curve revealed a cut-off point for pSUVmax of 11.0 with area under the curve (AUC) of 0.709 (95 % CI, 0.55- 0.96) with p = 0.026

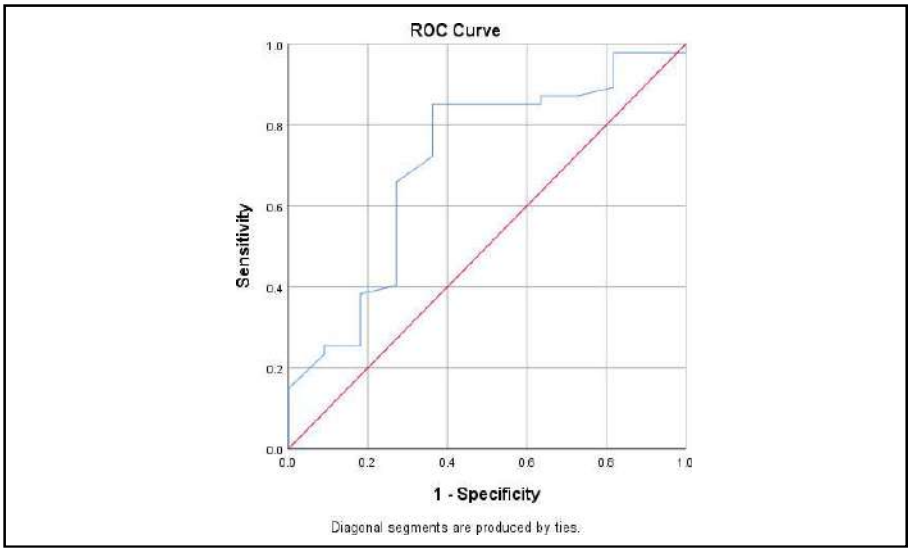


Figure 2. ROC curve plotted to obtain cut-off for pSUVmax to predict ALK mutation status

SUL_{peak} was lower in ALK positive patients (5.8 ± 3.1) compared to EGFR positive (9.1 ± 5.6) (p = 0.017) and wild type patients (9.7 ± 4.3) (p = 0.003), both of which were statistically significant. SUV_{mean} was also lower in ALK positive patients (4.4 ± 2.4) compared to EGFR positive (6.7 ± 3.6) (p = 0.024) and wild type patients (7.1 ± 3.4) (p = 0.006), both of which were statistically significant.

The data for $nSUV_{max}$ was obtained in patients who had regional nodal metastasis, i.e., in 78 out of 100 individuals (78 %), out of which 33 were EGFR positive (80.4 %), 11 were ALK positive (78.5 %) and 34 were wild type (75.6 %). $nSUV_{max}$ was lower in EGFR positive patients (7.7 ± 4.2) compared to ALK positive (9.5 ± 6.0) and wild type patients (8.3 ± 4.4), neither of which were statistically significant (p = 0.284 and p = 0.604 respectively).

The data for $mSUV_{max}$ was obtained in patients who had distant extra thoracic metastasis, i.e. in 63 out of 100 individuals (63 %), out of which 30 were EGFR positive (73.2%), 9 were ALK positive (64.2 %) and 24 were wild type (53.6 %). $mSUV_{max}$ was lower in EGFR positive patients (9.3 ± 5.2) compared to wild type patients (12.16 ± 4.2) which was statistically significant (p = 0.033).

Average SUV_{max} was calculated as average of $pSUV_{max}$, $nSUV_{max}$ and $mSUV_{max}$ in patients with nodal and distant metastases. Average SUV_{max} was lower in ALK positive patients (8.4 ± 5.1) compared to EGFR positive patients (9.3 ± 4.3) and wild type patients (10.5 ± 4.4) neither of which was statistically significant (p = 0.546 and 0.15 respectively).

Mann- Whitney U test was used to compare continuous variables with non-normal distributions, such as MTV and TLG. MTV and TLG were lower in patients with EGFR mutation compared to wild type patients which were statistically significant with p= 0.009 and p=0.013 respectively. TLG was lower in ALK positive compared to wild type patients, which was also statistically significant (p = 0.024).

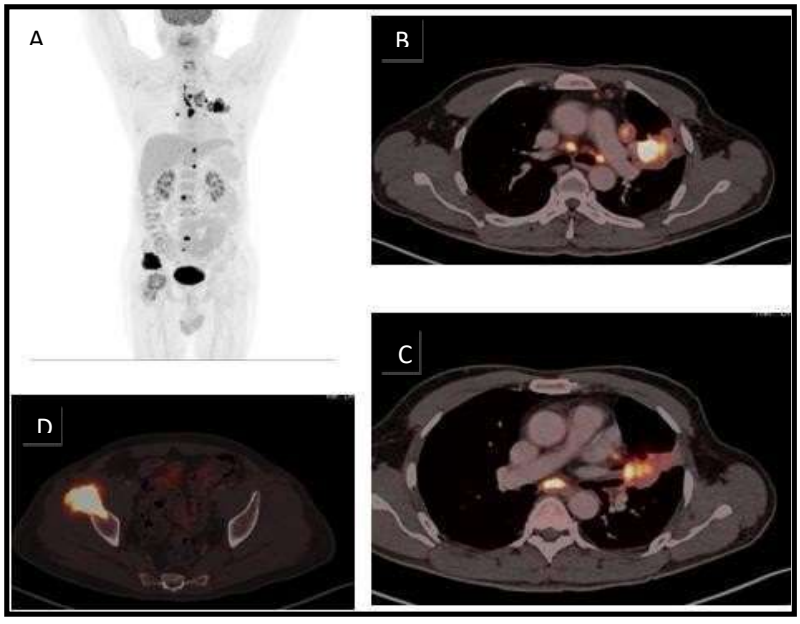


Figure 3. **A**- MIP image, **B**- Fusion image of F-18- FDG PET/CT in a 57 year old male with poorly differentiated lung adenocarcinoma of upper lobe of left lung, measuring 2.9 x 2.7 cms. SUVmax- 20.7, SULpeak- 13.7, SUVmean- 11, MTV- 6.3,TLG- 71 with nodal and distant metastases (Stage IVB). **C**- Metabolically most active regional subcarinal node and **D**- Distant skeletal metastasis in the right ilium. The patient tested positive for EGFR mutation.

Discussion

Since TKIs targeting EGFR and ALK have substantially improved survival in patients with NSCLC, genomic profiling has become the standard of practice for advanced NSCLC patients. For NSCLC, next-generation sequencing (NGS) is recommended to detect gene mutations or rearrangements [4]. However, tumor inaccessibility, insufficient sample tissue for identification, and patients' unwillingness to undergo invasive diagnostic techniques are all factors that can limit it. PET/CT has the added advantage of being a non- invasive method which can predict the status of EGFR and ALK mutations.

Reduced $pSUV_{max}$ was associated with EGFR positive status, according to Zhilei Lv et al. [5], and could be used with other clinical criteria to predict EGFR mutation status in some NSCLC patients who did not have access to genetic testing. Low $nSUV_{max}$ and $mSUV_{max}$ were likewise linked to the presence of an EGFR mutation. In our study, $mSUV_{max}$ was lower in EGFR positive patients (9.3 + 5.2) compared to wild type patients (12.16 + 4.2) which was statistically significant ($p = 0.033$), consistent with the above study. $pSUV_{max}$ was shown to be unrelated to ALK status in the above study. However, the study included all subtypes of NSCLCs like adenocarcinoma, squamous cell carcinoma and large cell carcinoma whereas our study included only adenocarcinomas. This might explain the discrepancy in these findings.

Hongyoon Choi et al. [6] found that ALK-positive lung cancer had higher glucose metabolism and faster nodal or distant metastases than EGFR-mutated and wild-type lung adenocarcinoma, implying that ALK rearrangement is more aggressive. The ALK positive group had a higher SUV_{max} of primary lesion than the EGFR positive and wild type groups (12 ± 7.86, 4.42 ± 3.61, and 5.96 ± 5.07, respectively). However, the study had a heterogeneous population with respect to stage, with 125 out of 156 (80.1%) from EGFR group belonging to stage I and II, 105 of 157 (66.9%) from wild type group belonging to stage I and II, but only 4 out of 18 patients (22.2%) from ALK positive group belonged to stage I and II. Also, the prevalence of ALK rearrangement in the patient population was not big enough to have statistical significance. Our study being prospective had no selection bias. Moreover, the patient sample was homogeneous with respect to the stage, with 92.7 % of EGFR group, 92.9 % of ALK group and 95.6 % of wild- type group belonging to stage III-IV. Also, 14% of the population was ALK positive which was considerably higher to assume statistical significance.

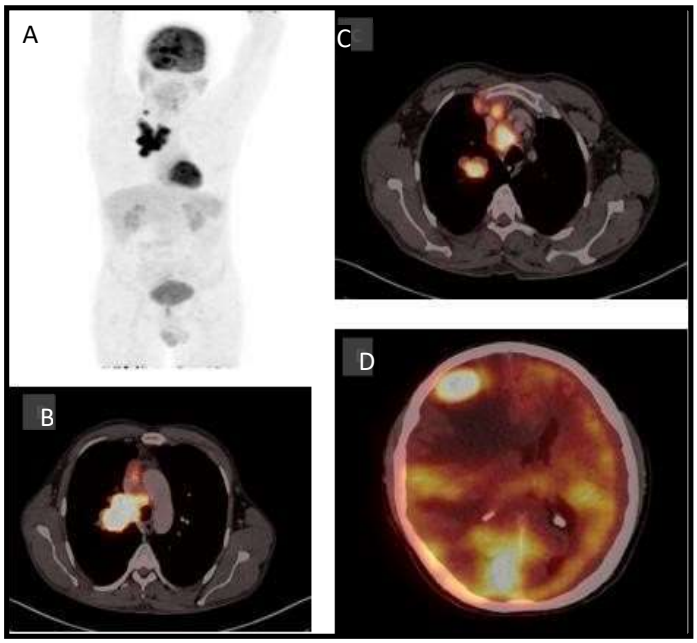


Figure 4. **A**- MIP image, **B**- Fusion image of 18F-FDG PET/CT in a 45 year old male with moderately differentiated lung adenocarcinoma of upper lobe of right lung, measuring 9.8 x 5.0 cms. SUV_{max}- 15.7, SUL_{peak}- 14.2, SUV_{mean}- 10.4, MTV- 51.3, TLG-534.8, with nodal and brain metastases (Stage IVB). **C**- Metabolically most active regional right upper paratracheal node and **D**- Distant brain metastasis in the right frontal lobe. The patient tested negative for both ALK and EGFR mutation.

According to Ao Liu et al [7], NSCLC patients with EGFR mutationsexhibited lower MTV than wild type patients ($p = 0.001$), which is similar to our findings. Patients with EGFR mutations had significantly lower SUV_{mean} values ($p = 0.031$) than those with wild-type EGFR. No statistically significant link was established between EGFR mutation positive and wild type patients in terms of SUV_{max}, similar to our study.

Bin et al. [8] conducted a retrospective study and found that 18F-FDG PET/CT metabolic characteristics combined with clinicopathological information had moderate diagnostic efficacy in predicting EGFR mutation status and were associated with prognosis in EGFR mutation positive and negative NSCLC, providing a pointer for personalized targeted therapy. It showed that EGFR positive patients had decreasedMTV and TLG, which matched our findings. EGFR positive patients had a lower SUV_{max} than wild type patients in this study.

Raymond et al [9] found increased FDG avidity in the EGFR wild type group with greater normalized SUV_{max} in a retrospective study. The normalized SUV_{max} was computed by dividing the lesion's SUV_{max} by the SUV of blood in the pulmonary artery. To discriminate between wild-type and EGFR mutation positive tumors, ROC curve analysis produced an area under the curve of 0.62, with a threshold > 5.0.

Lei et al. [10] found that measurements in FDG-PET/CT have limited predictive potential for the existence of EGFR mutation in lung adenocarcinoma. SUV_{max}, SUV_{mean}, SUV_{peak}, and SUVratio (the ratio of the primary tumor to the mediastinal blood pool) were all lower in EGFR-mutated tumors than in wild-type cancers. It hypothesized that EGFR positive pulmonary adenocarcinomas maybe physiologically more indolent than the EGFR-wild type ones, with reduced glucose metabolism.

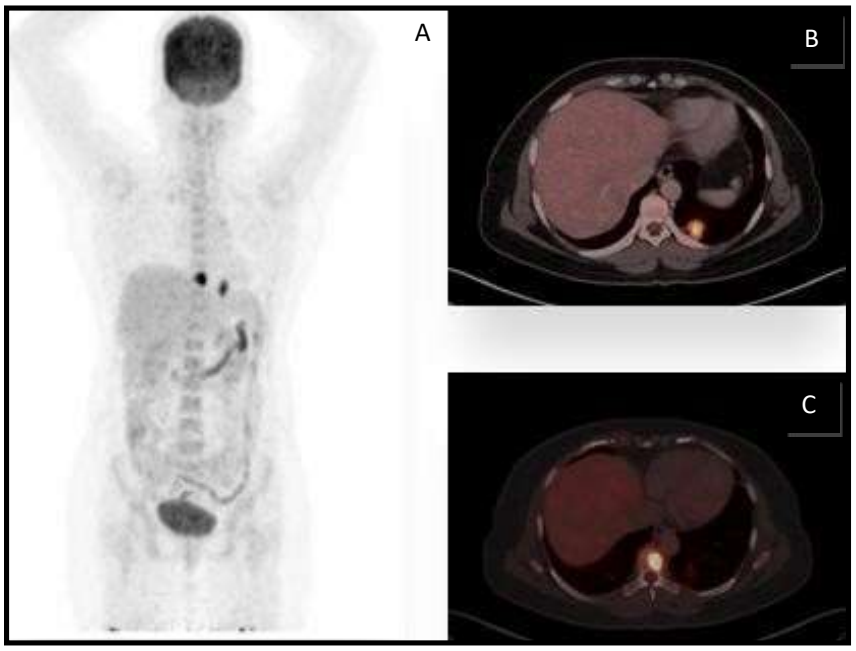


Figure 5. **A**- MIP image, **B**- Fusion image of 18F-FDG PET/CT in a 51 year old female with poorly differentiated lung adenocarcinoma of lower lobe of left lung, measuring 1.9x 1.8 cms. SUV_{max}- 9.8, SUL_{peak}- 6.9, SUV_{mean}- 5.9, MTV- 3.1, TLG- 18, with solitary skeletal metastasis (Stage IVA). **C**- Metabolically most active skeletal metastasis in **D**8 vertebra. The patient tested positive for ALK mutation.

According to a study by Kazuya Takamochi et al. [11], EGFR positive adenocarcinomas were physiologically indolent, with likely lower glucose metabolism than wild-type tumors. EGFR mutations were more common in tumors with lower SUV_{max}, while KRAS mutation status had no correlation with SUV_{max}.

SUV_{max} may be a predictive factor for EGFR mutation status, and MTV and TLG of primary tumors are promising prognostic indicators, according to a retrospective study by Il Ki Hong et al [12]. When EGFR positive tumors were compared to EGFR wild type tumors, the mean SUV_{max} was lower. Low SUV_{max} was found to be substantially linked to the presence of an EGFR mutation.

A possible explanation to these variances in the above studies can be that SUV_{max} can vary with different PET scanners, fasting time, plasma glucose level, and other factors, whereas MTV gives a more comprehensive overview of the overall metabolic activity of the tumor.

In our study, we found that various metabolic parameters were found to be reduced in both EGFR and ALK positive patients, when compared to wild- type patients. While ALK positive patients had a lower $pSUV_{max}$, SUL_{peak}, SUV_{mean} and TLG, EGFR positive patients had a lower $mSUV_{max}$, MTV, and TLG compared to wild type population. The $pSUV_{max}$ cutoff of ≤11 was found to be a predictor for ALK rearrangement. The mean pSUVmax for EGFR positive patients was 11.1 ± 5.6 and that of wild type patients was 11.8 ± 5.5 in comparison.

However, $pSUV_{max}$, SUL_{peak}, SUV_{mean} did not correlate with the presence of EGFR mutation. Considering the limitation of SUV_{max}, an alternative variable like metabolic tumor volume (MTV) and tumor lesion glycolysis (TLG) can be explored to assess the relationship between EGFR mutation status and PET/CT metabolic parameters, as our study demonstrated a lower MTV and TLG in EGFR mutated patients and lower TLG in ALK positive compared to wild type patients.

Conclusion

Based on this study, it was concluded that FDG- PET/CT can be used as a surrogate non-invasive tool that may provide important information in patients in whom tumor tissue is not available, although genetic testing continues to be the gold standard. PET/CT can help the clinician in assessing the disease prognosis, provide the appropriate treatment without delay, and better patient counseling for further management, as a surrogate marker which needs further support from trials. However, a multi-institutional trial on a larger population for a longer duration would further is needed for further modification of findings of the study.

Conflicts of interest

The authors declares that they do not have conflict of interest.

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