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The usefulness of 18F-FDG PET/CT in follow-up and recurrence detection for patients with lung carcinoma and its impact on the survival outcome

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Abstract

Background: We assess the usefulness of 18F-FDG PET/CT for detection of recurrent or residual tumor in post treatment patients with NSCLC and comparing the results with CECT, and we evaluate its impact to the clinical assessment and overall survival of lung cancer patients.

Results: A prospective study of 63 patients with potentially resectable NSCLC, were divided into 2 groups according to the initial staging of the disease and the early response to treatment.

Group A ($n=29$) patients were treated by curative treatment, and group B ($n=34$) patients were treated by palliative treatment.

Evaluation of patients was done during the follow-up period clinically every 3 months and by 18F-FDG PET/CT and CECT imaging at 6 months intervals.

In group A, 18F-FDG PET/CT correctly diagnosed all recurrent or residual tumors ($n=7$) whereas CECT diagnosed only 5 with 2 false negative cases.

In group B, 18F-FDG PET/CT correctly diagnosed all recurrent or residual tumors ($n=23$) whereas CECT diagnosed 16 patients with 7 false negative cases.

By comparison of 18F-FDG PET/CT and CECT in detection of residual or recurrent lung cancer ($n=30$), the sensitivity, specificity, PPV, NPV, and accuracy of 18F-FDG PET/CT were 100%, 92%, 92%, 100%, and 96% respectively, while of CECT were 72%, 95%, 94%, 79%, and 84% respectively in correlation with reference standard data. The calculated SUV max ranged from 2.1 to 4.9.

There was a significant difference in overall survival between patients in routine scan who had positive 18F FDG PET/CT result (median survival 18 months) and those who had negative result (median survival 45 months) ($P<0.0001$).

Conclusion: 18 F-FDG PET/CT plays an important role in distinguishing post treatment changes from tumor recurrence in patients with lung cancer. Follow-up or surveillance 18 F-FDG PET/CT is a prognostic indicator for overall survival of patients.

Keywords: Non-small cell lung cancer (NSCLC), 18F-FDG PET/CT, Overall survival

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Background

Lung carcinoma is one of the leading causes of cancer-related mortality worldwide. It is divided histologically into two main types: NSCLC accounts for 85% of cases and SCLC 10-15% of cases [1]. The overall 5-year survival rate for patients with lung cancer is 17.4% [2]. However, an important clinical problem in patients treated for lung cancer is the evaluation of treatment response and detection of recurrence. The post therapeutic anatomic and tissue alterations resulting from surgery and/or radiotherapy of lung cancer can make it difficult to discriminate necrotic tumor or fibrotic scar tissues from tumor relapse [3].

The follow-up radiological imaging by using response evaluation criteria in solid tumor (RECIST criteria) of lung cancer patients using CT with or without contrast media to detect tumor recurrence was widely accepted in determining treatment response. However, it depends on the size and mass changes occurred to the tumor post treatment, irrespective of the tumor viability, thus lowering its diagnostic performance with decreasing sensitivity and specificity for detection of cancer recurrence [4].

Although ^{18}F -FDG PET/CT may detect early functional changes occurred post treatment as well as structural changes, it is not included as routine in follow-up or surveillance after therapy [5].

The imaging principle of ^{18}F FDG PET/CT depends on the substantially different central metabolic pathways in malignant tissue. Thereby, most of the cancer cells show elevated levels of glucose uptake and thus produce high level of lactate compared to nonmalignant cells which may be detected by ^{18}F FDG PET/CT. The FDG uptake level can be assessed by using standardized uptake value (SUV) [6].

The aim of this study was to assess the usefulness of ^{18}F FDG PET/CT for detection of residual or recurrent tumors in post treatment NSCLC patients comparing the results with CECT, and to evaluate its impact to the clinical assessment and survival outcome of lung cancer patients.

Methods

Selection of patient and their preparation

This prospective study included 63 patients with potentially resectable NSCLC with age ranged from 49 to 75 years. Patients were examined at our radiology department over a period from February 2017 to February 2021. According to the initial staging of the tumor and the early response to treatment, all patients were divided into 2 groups: Group A, patients were treated with curative treatment and, group B patients were treated with palliative treatment.

^{18}F FDG PET/CT and CECT were performed to all patients as requested.

Serum creatinine was asked to be below 2 mg/dL prior to the study and the blood glucose level (< 160 mg/dL) was controlled before the date of imaging to avoid FDG misinterpretation.

The patients were fasted for at least 6 h prior to the scan. They were requested to rest in a quiet room and try to avoid vigorous movement and talking as minimal as possible to minimize physiological uptake of FDG.

Informed consent has been taken from all the patients as according to the ethical committee regulations.

Technique

^{18}F -FDG PET/CT is performed using PET/CT scanner (Discovery STE; GE Healthcare, Boston, USA). In total, 5.5 MBq/kg ^{18}F -FDG dose was injected intravenously 60 min before starting the scan. A PET emission scan was performed over several bed positions from 5-7 for 2 min per bed position with axial field of view of 21.6 cm per bed position and in plane spatial resolution of 2 mm from the base of the skull down to the mid-thigh at 2 min per bed position.

The following diameters were used in performing the CECT, 120 kV, 350 mAs, 0.5 s tube rotation, slice thickness of 5 mm, with 8 mm table feed, and 3 mm incremental reconstruction. Transaxial PET and CT images were reconstructed, fused, and reformed into coronal and sagittal images, and data were generated. The SUV_{max} in the volume of interest was measured.

The ^{18}F FDG PET/CT images were interpreted via two experienced radiology consultants with more than 5 years of experience with inter-observer agreement.

Two experienced radiology consultants, more than 5 years of experience, interpreted the CECT images with inter observer agreement.

The readers were blinded to each other and reports were compared. A comparison between ^{18}F FDG PET/CT and CECT findings was done and it was pathologically confirmed by biopsy, clinical evaluation, and subsequent imaging progression of patients.

Images analysis

Visual analysis

Any focus of elevated FDG metabolism, and not located in areas of normal FDG uptake, was considered positive.

Quantitative analysis

^{18}F -FDG PET/CT was measured by SUV_{max} , we manually placed the region of interest on each lesion of abnormal uptake then it was calculated.

Statistical analysis

Sensitivity, specificity, positive and negative predictive value (PPV and NPV), and accuracy of ^{18}F FDG PET/CT and CECT for detection of tumor recurrent and/or

residual tumor were calculated and compared using McNemar *T* test. *P* value was set to be statistically significant when it is ≤ 0.05 . The SUV_{max} of tumor was quantitatively and qualitatively evaluated. All the collected data were loaded and coded by using the Statistical Package for Social Sciences (SPSS version 22).

Patient's overall survival measures

The overall survival of the patients in routine scan was measured as the time interval between the follow-up 18F FDG PET/CT scan and the end of data collection. The statistical analysis was done to determine the relationship between the follow-up 18F FDG PET/CT results and overall survival of patients.

Results

In this prospective study, we analyzed 63 patients with potentially resectable NSCLC with age ranged from 49 to 75 years. Patients were examined at our radiology department over a period from February 2017 to February 2021. The final staging of the disease was as follows: Stage I, 10 patients; stage II, 11 patients; stage IIIA, 18 patients; and stage IIIB, 24 patients. Serum creatinine was (<2 mg/dL) and the blood glucose level (<160 mg/dL) before the imaging.

The therapeutic regimens ranged from surgery/and or radiotherapy and occasionally associated with chemotherapy (Table 1).

According to the initial staging of the tumor and the early response to treatment, all the patients were divided into 2 groups:

Group A ($n=29$), in this group, patients were treated by curative treatment, 21 patients with stages I and II and 8 patients with stage IIIA. None of these patients showed a persistence intrathoracic radiological abnormality for 3 months after the end of treatment.

Group B ($n=34$), in this group, patients were treated by palliative treatment. All of these patients showed persistence intrathoracic radiographic abnormality for 3 months after the end of treatment.

Follow-up assessment was performed more than 6 months after the primary treatment completion. Each patient was clinically evaluated every 3 months during the treatment follow-up period. 18F FDG PET/CT and CECT imaging was performed at 6 months intervals for 6–36 months, however, if the patient presented by suspicious symptoms or if the radiological imaging suggested residual or recurrence of the tumor, a biopsy was obtained and clinical and radiological follow-up was performed.

18F FDG PET/CT and CECT imaging revealed

In group A, all recurrent tumors ($n=7$) were correctly diagnosed by 18F FDG PET/CT (high FDG uptake) whereas CECT correctly detected recurrent tumors in 5 patients with 2 false negative cases, as metastatic mediastinal lymphadenopathy were not detected by CT (Figs. 1 and 2).

18F FDG PET/CT and CECT correctly identified the regression of tumor in 21 of 22 patients. Detection of one false positive case by 18F FDG PET/CT imaging in a patient with radiation pneumonitis and one false positive case by CECT was noted (Table 2).

The sensitivity, specificity, PPV, NPV, and accuracy of 18F FDG PET/CT in detecting tumor recurrence in correlation with reference standard data were 100%, 97%, 93%, 100%, and 98% respectively. The accuracy of CECT was 91%.

In group B, all recurrent or persistent cases ($n=23$) of lung tumor revealed increase FDG uptake by 18F FDG PET/CT with no false negatives. CECT results revealed stable appearance with no regression of the tumor in 16 cases while 7 cases were false negative (Fig. 3).

Eleven patients showed absence of recurrent tumors for 15–36 months after treatment, they were correctly identified by 18F FDG PET/CT in 9 cases and by CECT in 10 cases.

In this group of patients, 18F FDG PET/CT showed two false positive cases (1 infectious process and 1 radiation pneumonitis) and CECT showed one case false positive as it showed tissue changes suspicious for tumor recurrence (Table 3).

The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT in detecting tumor recurrence in correlation with reference standard data were 100%, 81%, 92%, 100%, and 94% respectively. The accuracy of CECT was 78%.

By comparison of both groups for 18F FDG PET/CT and CECT in detection of residual or recurrent lung carcinoma revealed, sensitivity, specificity, PPV, NPV, and accuracy of 18F FDG PET/CT were 100%, 92%, 92%, 100%, and 96% respectively, while of CECT were 72%, 95%, 94%, 79%, and 84% respectively in correlation with reference standard data.

Table 1 Treatment regimen of groups A and B patients

	Treatment regimen	Patient number
Group A ($n=29$)	Surgery	16
	Surgery+radiotherapy	6
	Surgery +chemotherapy	6
	Chemotherapy +radiotherapy	1
Group B ($n=34$)	Radiotherapy	16
	Radiotherapy+chemotherapy	14
	Surgery +chemotherapy	4

Fig. 1 (a-b) 56-year-old female with recurrent lung carcinoma 18F-FDG PET/CT was performed 1 year post treatment, revealed 3.2 cm APx2.7 cm wide FDG avid mass (SUV_{max} 3.4) in the posterior segment of right upper lung lobe (arrow). Right retrocaval pretracheal lymph node with low-grade activity tumor bearing lymph node was noted (a). CT imaging revealed atelectasis and/or pneumonitis measuring 3.2 cm APx2.7cm wide at the posterior segment of right upper lung lobe with no metastatic lymphadenopathy detected (b)

The calculated SUV max ranged from 2.1 to 4.9.

The overall survival analysis

The 18F FDG PET/CT scans revealed from 63 patients were grouped as negative or positive reports for tumor recurrence or metastasis.

18F FDG PET/CT scans for recurrence or metastasis display negative result in 33 patients and positive in 30 patients.

Of the negative 18F FDG PET/CT results, 40% were obtained 6-24 months after completion of treatment and 60% more than 24 months.

Of the positive scans, 45% were obtained 6-24 months after completion of treatment and 55% more than 24 months.

Fig. 2 (a-d) 72-year-old male with recurrent lung tumor post therapy 18F-FDG PET/CT revealed 3.6 cm APx2.5 cm wide medial left upper lobe (SUV_{max} 4.9) speculated mass with surrounding non FDG avid atelectasis (arrow). Contiguous left hilar metastatic lymphadenopathy (SUV_{max} 4.9) was detected (**a, b**). CT revealed atelectasis measuring 3.6 cm APx2.5cm wide at the medial left upper lobe with no hilar metastatic lymphadenopathy detected (**c, d**)

A significant difference with P value <0.0001 has been revealed in overall survival by using the Kaplan-Meier analysis between the patients in routine scan who had positive 18F FDG PET/CT result (median survival 18 months) and those who had negative result (median survival 45 months) (Fig. 4).

Discussion

The early detection of disease recurrence and assessment of the therapeutic response in patients treated for lung cancer has been of great importance [7].

18 F-FDG PET/CT is a valuable routine imaging tool in the diagnosis and staging of lung cancer; however, its

Table 2 Group A ($n=29$) follow-up imaging results (correlation with final diagnosis)

	18 F-FDG PET/CT	CECT
Remission		
True negative	21	21
False positive	1	1
Recurrent or residual		
False negative	0	2
True positive	7	5

value in follow-up and surveillance is still controversial [8]. In this study, we assess the usefulness of 18 F-FDG PET/CT in differentiating post treatment changes in patient with NSCLC from tumor relapse comparing the results with CECT, and we evaluate its impact to the clinical assessment and overall survival of lung cancer patients.

The present study found that 18 F-FDG PET/CT was more accurate than CECT in distinguishing persistent or recurrent tumor from fibrotic scar tissue in patients treated for NSCLC. All of the recurrent tumors were correctly diagnosed by 18 F-FDG PET/CT, 7 patients in group A (patients were treated with curative treatment) and 23 in group B (patients were treated with palliative treatment). By comparison of 18 F-FDG PET/CT and CECT in detection of residual or recurrent lung cancer, the sensitivity, specificity, PPV, NPV, and accuracy of 18 F-FDG PET/CT were 100%, 92%, 92%, 100%, and 96% respectively while those of CECT were 72%, 95%, 94%, 79%, and 84% respectively, in correlation with reference standard data. The calculated SUV_{max} ranged from 2.1 to 4.9.

These results were in concordance with a previous meta-analysis done by You J et al. who reported that 18

Fig. 3 (a-d) 65-year-old female with 2 years status post chemotherapy 18F-FDG PET/CT revealed stationary course of the left lateral upper lobe chest wall mass (7.3 cmAPx5.7 cm vertical distance x3.5 cm wide) with coarse dystrophic calcification and underlying reconstituted rib cage. Lesion demonstrates low-grade FDG activity (SUV_{max} 1.4) (arrow) (a, b). On follow-up, new 1 cm FDG avid right posterior lung nodule (SUV_{max} 2.1) (arrow) consistent with neoplasm was detected (c, d)

Table 3 Group B (n=34) follow-up imaging results (correlation with final diagnosis)

	18 F-FDG PET/CT	CECT
Remission		
True negative	9	10
False positive	2	1
Recurrent or residual		
False negative	0	7
True positive	23	16

F-FDG PET/CT is a superior modality for detecting recurrent lung tumor compared with other conventional imaging modalities including chest X-ray, CT, bone scintigraphy, and MRI. The pooled sensitivity and specificity were found to be 90% and 90% respectively for 18 F-FDG PET/CT and 78-80% respectively for conventional imaging [9].

Sawada S. et al. and Alexander J. et al. just compared 18 F-FDG PET/CT and CECT in detecting recurrent or persistence tumor during follow-up period, they concluded 97-100% sensitivity and 62-

Fig. 4 Kaplan-Meier survival analysis showed significant difference of the overall survival of patients with 18F-FDG PET/CT positive and negative results for tumor

100% specificity of 18 F-FDG PET/CT. However, they considered it for follow-up assessment when it is performed more than 6 months after primary treatment completion [10, 11].

The present study demonstrated that 18 F-FDG PET/CT positive result for tumor relapse were accompanied with decreased overall survival of patients ($P < 0.0001$) regardless of the timing for performing the scan during the follow-up or surveillance period. This agreed with Coche E. published research which found a significant negative relationship between overall survival and positive 18 F-FDG PET/CT results [12].

Barnett SA. et al. demonstrated that 18 F-FDG PET/CT was of a significant prognostic indicator of overall survival regardless of the timing of the scan; hence, it may lead to a significant change in management of lung cancer patients [13].

In controversy, a previous study done by Ettinger DS et al. stated that 18 F-FDG PET/CT is better performed when there is clinical suspicious of recurrent tumor or metastases and according to the patients clinical symptoms or laboratory examinations findings. They stated that 18 F-FDG PET/CT as routine surveillance without any clinical suspicious should be discouraged [14]. However, other authors Budak E et al. concluded that 18 F-FDG PET/CT could potentially become an alternative to conventional follow-up modalities after treatment therapy [15].

Limitations for the present study were the small number of patients and the high cost of the technique which justify further research.

Conclusion

18 F-FDG PET/CT plays an important role in distinguishing post treatment changes from tumor recurrence in patients with lung cancer. Follow-up or surveillance 18 F-FDG PET/CT is of great value for overall survival of patients. However, the prognostic value and the cost effectiveness in follow-up need to be further investigated by large scale multi-center study.

Abbreviations

NSCLC: Non-small cell lung cancer; 18 F-FDG PET/CT: 18F fluorodeoxyglucose positron emission tomography/computed tomography; CECT: Contrast-enhanced computed tomography; SUV: Standard uptake value; PPV: Positive predictive value; NPV: Negative predictive value

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Author's contributions

The single author is solely responsible to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. The author 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

This study was approved by the Research Ethics Committee of the Faculty of Medicine at October 6 University, reference number not applicable. All patients gave written informed consent to participate in this study which was approved by the Research Ethics Committee of the Faculty of Medicine at October 6 University.

Consent for publication

All patients included in this study gave informed consent to publish the data contained within this study.

Competing interests

The author declares that she has no competing interests.

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