ORIGINAL ARTICLE

Mapping 18F-Fluorodeoxyglucose Metabolism Using PET/CT for the Assessment of Treatment Response in Non-Small Cell Lung Cancer Patients Undergoing Epidermal Growth Factor Receptor Inhibitor Treatment: A Single-Centre Experience

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ABSTRACT

Introduction: Specific mutations in the epidermal growth factor receptor (EGFR) characterize a subgroup of non-small cell lung cancer (NSCLC) patients that may be highly responsive to receptor inhibitor therapy. 18F-FDG PET/CT scans can map the glucose metabolism and treatment response of NSCLC. Therefore, we aimed to assess the pattern of metabolic response and outcome of inoperable NSCLC treated with epidermal growth factor receptor (EGFR) inhibitors, using 18F-FDG PET/CT scan. **Methods:** A retrospective study of inoperable NSCLC patients on EGFR inhibitor treatment that were referred for wholebody18F-FDG PET/CT scans was conducted based on cases scanned from January 2011 to June 2014. Comparison was made among serial attenuation-corrected fused PET/CT images for all study patients throughout the course of their treatment. Comparison based on PERCIST criteria was categorized into 4 levels ie. complete response (CMR), partial response (PMR), stable disease (SMD), progressive metabolic disease (PMD). **Results:** Overall, there were 5 patients identified, mean age: 57.4 years old +/- 2.9 years; The median survival time from initiation of EGFR inhibitor treatment to death was 17 months. Two patients showed initial partial metabolic response (PMR), two had progressive metabolic disease (PMD) and one had complete metabolic response (CMR) after the initiation of treatment. The patient with initial CMR had relapse and PMD 5 months later. Majority of patients eventually succumbed to their illness. **Conclusions:** Wholebody18F-FDG PET/CT is able to assess metabolic treatment response of NSCLC towards EGFR inhibitor treatment.

Keywords: Lung cancer, Positron emission, Targeted therapy

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INTRODUCTION

Non-small cell lung cancer (NSCLC) constitutes nearly 85% of lung cancers, whereby adenocarcinomas account for the majority of cases (1). Strategic planning for commencement of cytotoxic therapy is required once the diagnosis of advanced adenocarcinoma is made. This necessitates advanced molecular testing to detect anaplastic lymphoma kinase (ALK) rearrangements and epidermal growth factor receptor (EGFR) mutations which help to prognosticate the likelihood of tumuor responsiveness to a certain targeted therapy (2). Epidermal growth factor receptor (EGFR) is cell surface protein that binds to epidermal growth factor, which then acts as a docking site to propagate the receptor to become dimerised and leads to autophosphorylation of tyrosine and stimulates cell proliferation. This also plays a role in cell survival by regulating intracellular downstream pathways(3).

Mutations in the gene that encodes the EGFR protein leads to lung cancer. Therefore, development of targeted therapy drugs that inhibit this receptor can hinder dysregulated cell proliferation, thus control disease progression. Targeted therapy utilizes drugs that are specially designed to selectively target molecular pathways that are involved in the expression of aggressive phenotype in lung cancer cells. Hence, the exposure to toxic effects by surrounding normal cells is minimised. Novel cytotoxic agents for targeted therapy

include tyrosine kinase inhibitors (TKIs) directed against the EGFR. TKIs are from quinazolinamine class and inhibit the tyrosine kinase activity of the EGFR protein docking site by competing with ATP for the ATP-binding site (4).

Nevertheless, many patients inevitably develop acquired resistance and show disease progression. EGFR inhibitors can often reduce tumour size or even cause remission for several months or more. Unfortunately, these types of targeted therapy have been known to cause further mutations in the EGFR gene, such as T790M mutation which leads to treatment resistance (5, 6). Several large phase II clinical trial studies have demonstrated initial response to the TKIs including the reversible inhibitors, erlotinib and gefitinib (7, 8). Some of these patients show initial radiologically-assessed morphological response rates of >60 % and improved progression free survival compared with treatment using conventional chemotherapy, only later to exhibit insensitivity to EGFR inhibitors (9, 10).

Positron emission tomography/ computed tomography (PET/CT) can be especially helpful in addressing the issue of early detection of treatment resistance buy mapping the altered glucose metabolism of cancer cells. By using 18F-Fluorodeoxyglucose (18F-FDG), which is a glucose analogue, the in vivo cell metabolism can be imaged by the detection of intracellular photons emissions of trapped 18F-FDG molecules in cancer cells that have altered glucose metabolism but cannot enter the glycolysis pathway, thus getting trapped within cancer cells. As a matter of fact, normal physiology of cells is to undergo anaerobic glycolysis via the Krebs cycle in mitochondria. Conversely, in cancer cells a phenomena known as the Warburg effect, propagates increased glucose uptake into the cells allowing the cells to utilize glucose by a paradoxical 'aerobic' glycolysis driven by oncogenes thus producing lactic acid in the cytosol (11) which rely primarily on mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, most cancer cells instead rely on aerobic glycolysis, a phenomenon termed \" the Warburg effect. \" Aerobic glycolysis is an inefficient way to generate adenosine 5\u2032-triphosphate (ATP. Alternative theory also suggests that inhibition of mitochondrial anaerobic glycolysis impairs formation of reactive oxygen species and leads to reduced glutathione formation which hampers intracellular defence against damage and cell apoptosis, thus promoting cancer cell growth.

This shunting of glucose into alternative pathways are catalysed by the aberrant form of pyruvate kinase enzyme, M2-PK that increases production of the building blocks of cell formation and accelerates cell proliferation leading to proliferation of cancerous tumours (12). Furthermore, Studies show that absence of metabolic response to neoadjuvant chemotherapy correlates with poor pathologic response, and a favourable 18F-FDG PET/CT response appears to be associated with improved survival (10)combined-modality therapy, and early detection of recurrence. Here, we review the current literature on these aspects of PET in the management of NSCLC. FDG-PET, particularly integrated (18).

Advanced, inoperable non-small cell lung cancers are generally treated with platinum based systemic chemotherapy. However, specific mutations in the epidermal growth factor receptor (EGFR) characterize a subgroup of patients that may be highly responsive to receptor inhibitor therapy. 18F-Fluorodeoxyglucose PET/CT imaging is considered the modality of choice to assess treatment response in NSCLC patients (13). Our objective was to assess the pattern of metabolic response as well as the outcome of inoperable non-small-cell lung cancer patients that have undergone targeted treatment with epidermal growth factor (EGFR) inhibitors and followed up using 18F-FDG PET/CT.

MATERIAL AND METHODS

A retrospective study was conducted based on data from inoperable, NSCLC patients on EGFR inhibitor treatment and re-staged with wholebody18F-FDG PET/CT scan at the Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia from January 2011 to June 2014. All patients consented to the procedures and institutional ethical clerance was waived due to the nature of the study. We initially identified 6 patients, but one patient had to be dropped out of the study, as he did not have a comparison scan done at our centre. Thus, five patients (3 men; 2 women) were identified as fulfilling the study criteria. These patients had underwent serial contrast-enhanced CT (CECT) scans followed by 18F-Fluorodeoxyglucose positron emission tomography scans. All patients were kept fasted for the PET/CT examination and their fasting blood sugar (FBS) levels were checked prior to the scan.

The patients were administered with 18F-FDG dosage based on their body weight and the injected dose ranged from 7.89 to 11.25 mCi (mean 9.70 +/- 1.22). Patients were kept rested in a dim quiet room, which allowed for 18F-FDG uptake time, mean uptake time was 32.0 +/- 4.5 minutes. All scans were performed following standard protocol using Siemens Truepoint Biograph 'TrueV®' comprising Lutetium Oxyorthosilicate (LSO) scintillator crystal camera and 64 slice multidetected CT scanner. All images were analysed separately followed by combined analysis of attenuation-corrected fused PET/CT images on a Syngo Multi-Modality Workstation. Standardized uptake values (SUV_{max}), and anatomical tumour size were measured for the lesions detected and development of never sites of metastases were recorded.

Inclusion criteria for the study was that all the NSCLC patients who were initially treated with platinum-based chemotherapy and subsequently treated with EGFR inhibitors as a second line treatment and underwent baseline and follow up scans at our centre. They were non-selectively treated with EGFR inhibitors irrespective of their EGFR receptor status. We excluded cases that did not have a follow up scan at our centre for comparison and assessment of treatment response.

All patients then underwent PET/CT scan in a hybrid scanner and the images were analysed separately for CT images and fused PET/CT images and interpreted by consensus. Comparison was made among baseline and serial attenuation-corrected fused PET/CT images for all study patients throughout the course of their treatment. The lesion sizes on CT image alone and PET / CT images as well as the maximum standardized uptake values (SUV_{max}), were measured. The SUV_{max} values of target lesions at baseline were measured using a standard region of interest (ROI) measurement and compared with consecutive follow up PET/CT images. Presence of new metastatic lesions was also recorded. Analysis based on PERCIST criteria was categorized into 4 levels ie. complete metabolic response – CMR – resolution of uptake in target lesion to below the mean uptake level of the liver, partial metabolic response – PMR – reduction of uptake of target lesion to approximately 30% of initial uptake, stable metabolic disease - SMD, and progressive metabolic disease – PMD – increased uptake of target lesion to approximately 30% or more compared to baseline uptake. Overall survival was calculated from date of diagnosis to date of death.

RESULTS

We identified 5 patients diagnosed with Stage III and IV inoperable adenocarcinoma of the lung and treated with EGFR inhibitors. Three patients had three serial PET/CT scans, one patient had a baseline and comparison scan and another patient had 5 serial scans for comparison. Overall there were 16 PET/CT scans analysed for changes in SUV_{max} values in this study (Figure 1). Patients ranged from 53 – 61-years old (mean age: 57.4 +/- 2.9 years), the male: female ratio was 2:1. FBS levels of the patients ranged from 3.6 – 4.5 mmol/L.

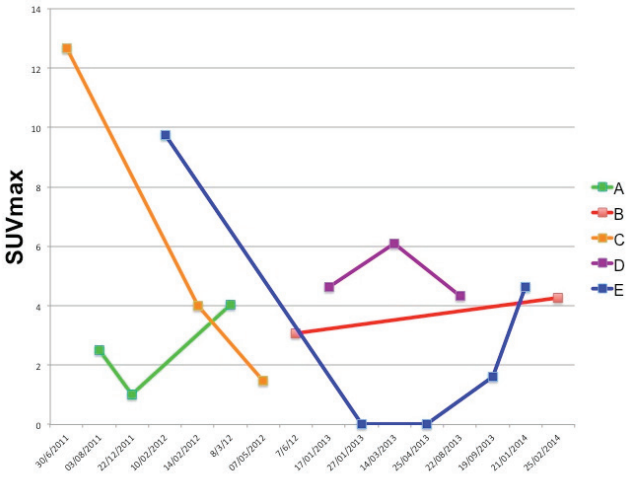

Figure 1: Line chart showing the changes in SUVmax values during serial follow up PET/CT scans of five non-small cell lung cancer patients A, B, C, D and E undergoing EGFR inhibitor treatment.

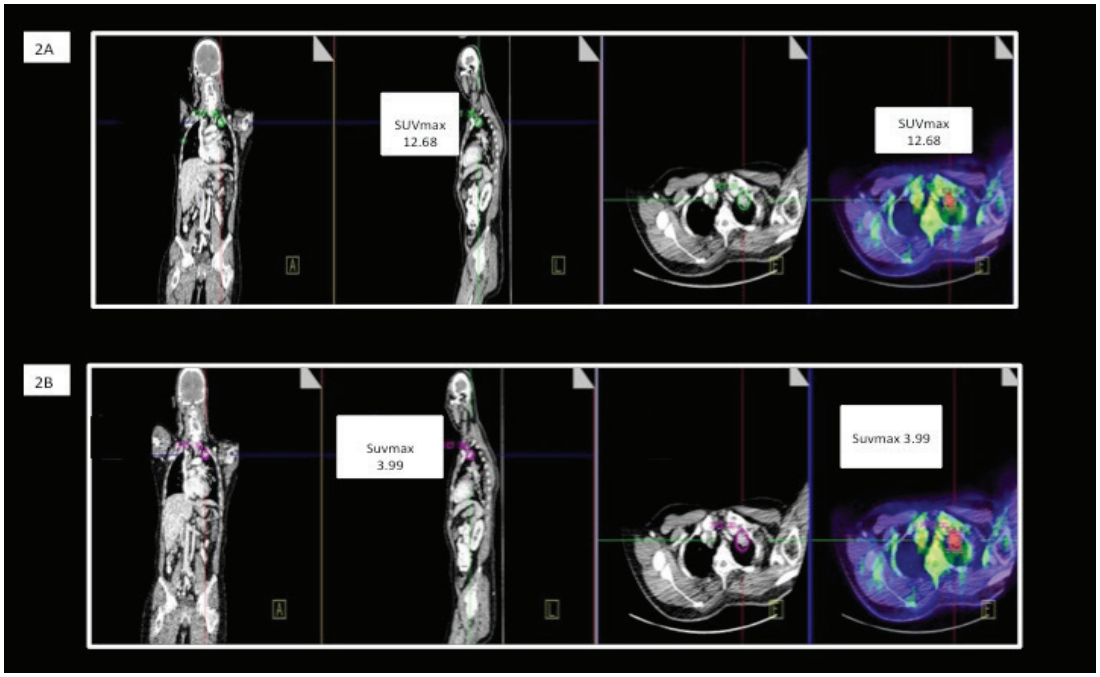

Figure 2: A 58-year old gentleman, diagnosed with inoperable NSCLC had been treated with 2nd line EGFR inhibitor therapy. (A): Initial PET/CT detected a left apical lung mass which showed avid FDG uptake, SUV_{max} 12.68g/mL. (B) Follow-up PET/Ct after several months of therapy detected reduction in SUV_{max} to 3.99g/mL, without a significant change in tumour size, demonstrating a partial metabolic response (PMR).

Based on Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) and PET Response Criteria in Solid Tumors (PERCIST), version 1.0; the largest diameter of target lesions at baseline was 6.0 cm and the smallest target lesion diameter was 3.0 cm. The SUV_{max} for the main target lesions in the lung at baseline scan ranged from 2.5 g/mL – 12.68 g/mL.

Two patients showed initial partial metabolic response (PMR) as demonstrated by the green and orange lines in Figure 1; two had progressive metabolic disease (PMD) as demonstrated by the purple and red lines in Figure 1 and one had complete metabolic response (CMR) after the initiation of treatment, which was demonstrated by the blue line in Figure 1. However, the patient with initial complete metabolic response (CMR) developed treatment resistance and PMD 5 months later. The patient had developed new small lung nodules and metastatic liver lesions that were inconspicuous on CT scan alone. Furthermore, one of the patients with initial PMR had good response to treatment and remained as stable metabolic disease (SMD). This patient had survived for more than 24 months after being treated with EGFR inhibitor therapy. However, the majority of patients eventually developed treatment resistance and succumbed to their illness. The median survival time from initiation of EGFR inhibitor treatment to death was 17 months.

Two patients showed complete resolution of the main target lesion, however had persistent metastatic deposits. Subsequently, progressive metabolic disease was noted within one year of undergoing therapy. One of the patients who showed initial partial metabolic response subsequently had aggressive tumour recurrence within 5 months of treatment (primary tumour had size: 3.1cm,SUV_{max} :12.68g/mL reduced to size:1.66cm; SUV_{max} 3.99g/mL but subsequently there was increase in size to 1.97cm with new FDG avid

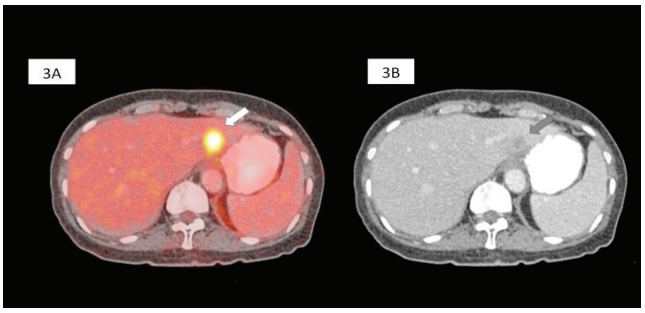

Figure 3: A 62-year old lady with Stage IV NSCLC had a PET/CT scan done for re-staging (A): There was FDG hypermetabolism detected at segment VIII of the liver, SUV_{max} 10.4g/mL (white arrow) (B) However, on axial plane whole body CT scan image in soft tissue window (W:250, L:50) at the level of the liver showed a vague hypodense focus (grey arrow) at the corresponding site in keeping with site of metastasis (inconspicuous on CT compared to PET).

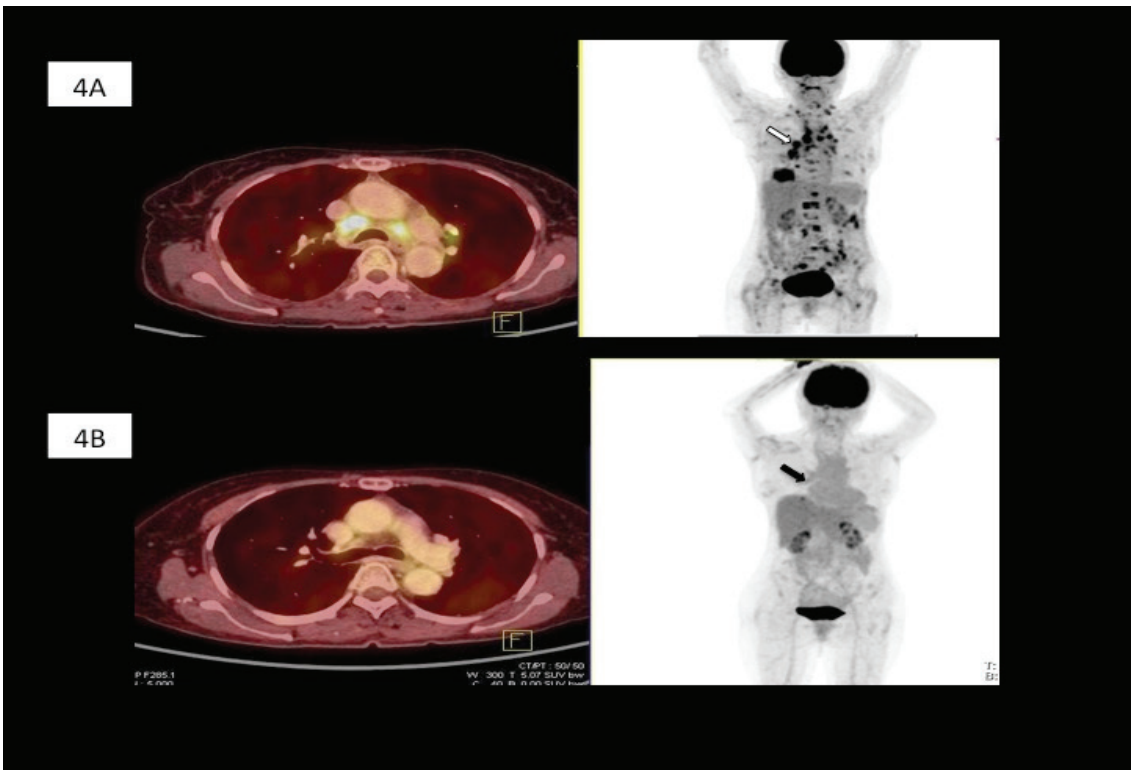

Figure 4: (A) Baseline PET/CT revealed a 61-year old lady with Stage IV NSCLC to have multiple lung metastases and mediastinal lymphadenopathy (white arrow). (B) Follow-up PET/CT demonstrated remarkable response to treatment with resolution of the lymphadenopathy (black arrows) no abnormal FDG uptake throughout the body in keeping with complete metabolic response (CMR).

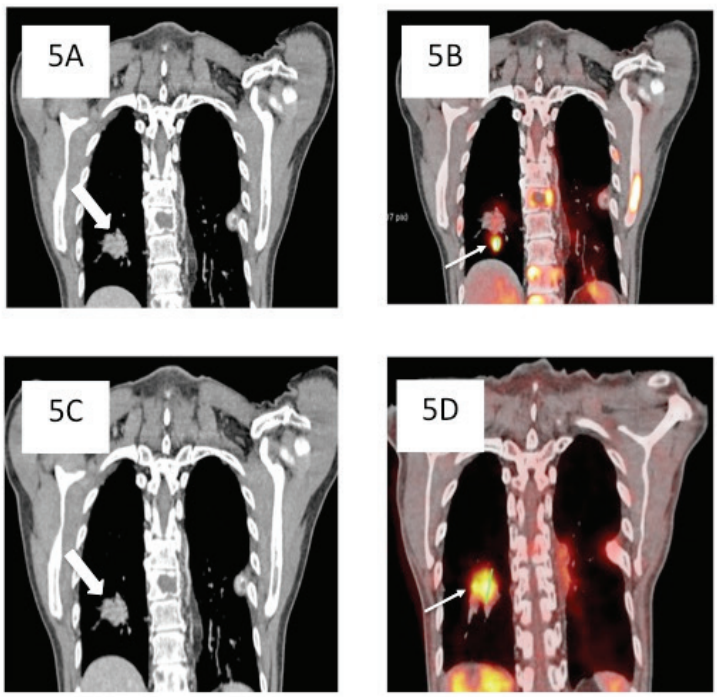

Figure 5: (A): Right lower lobe lung mass on CECT (thick white arrow), (B) True metabolically active lesion on coronal PET/CT images (thin white arrow) however the signal uptake is seen slightly lower than the actual lesion due to misregistration artifact; (C) CECT scan showing stable disease (thick white arrow) as assessed using RECIST criteria due to similar diameter of the lesion in baseline and follow up scans (D) PET/CT is more accurate to pick up the increasing trend of SUV_{max} reading and wider area of FDG hypermetabolism (thin white arrow), therefore confirming progressive metabolic disease (PMD) by PERCIST criteria.

mediastinal lymphadenopathy , SUV_{max} :4.1 to 10.5g/mL) in keeping with progressive metabolic disease (Figure 2). Nevertheless, PET/CT demonstrated good overall survival whereby, the average time of survival after EGFR inhibitor treatment was 20.0 months +/- 5.9 months.

DISCUSSION

The management of non-small cell lung cancer often requires a multimodality approach to accurately diagnose, stage, and treat patients. PET/CT can be a non –invasive tool to study in vivo altered cell metabolism and aid in early detection of treatment response. By using the PERSIST criteria which takes into account the maximum standardized uptake values (SUV_{max}) in the liver to assess percentage of reduction of metabolic activity in the tumour as well as to assess the temporal changes of the dynamic SUV readings over the course of the treatment (14)the Response Evaluation Criteria in Solid Tumors (RECIST, clinicians are able to quantitatively monitor treatment response. Images can also be analysed according to RECIST criteria which is a set of published guidelines to assess cancer patients' morphological response to treatment (15)many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1. It includes definitions of the minimum size of measurable lesions, instructions about how many lesions to follow up and measure, and the use of a single dimensional measurement for evaluation of overall tumor burden (16).

Additionally, functional imaging which measures the altered glucose metabolism in cancer cells provides more accurate detection of disease progression compared to morphological assessment alone. For example, one of our subjects had small liver metastases (SUV_{max} 4 – 10 g/mL), which was only picked up on PET/CT imaging (Figure 3). On further scrutinizing the CT scan images, an almost imperceptible focus of ill-defined hypodensity was noted in the corresponding location. This demonstrates that PET/CT is sensitive to pick up lesions earlier by detecting the signals of altered metabolism as compared to the anatomical changes, which are usually detected at a later stage.

Furthermore, in our study, a subject with Stage IV adenocarcinoma lung showed complete metabolic response (Figure 4) and remission of her primary lesion, within 6 months post-treatment using EGFR inhibitors. This corresponds to other previous studies whereby non-smokers, women and patients of Asian origin have shown to benefit from EGFR inhibitor targeted treatment

for NSCLC (17). However, this patient developed new metastatic lesions 5 months later and died before her treatment regime could be altered. This illustrates that early detection of resistance is necessary to make a timely decision for change in treatment regime. Some studies have identified markedly reduced insulin-like growth factor (IGF)-binding protein 3, whereby administering insulin-like growth factor 1 receptor (IGFIR)-specific monoclonal antibody could prevent further cell growth and thus prevent tumor recurrence (18).

Apart from improved lesion conspicuousness on PET/CT, this modality also gives improved accuracy in detecting the truly metabolically active tumour size as illustrated in the case of a 68-year old gentleman, who had a right lower lobe adenocarcinoma and follow up scans were done to assess treatment response. Although there was no significant changes on the tumour size on CT scan as assessed by the RECIST criteria, there was significant increase in the SUV_{max} value and wider area of FDG hypermetabolism, indicating progressive metabolic disease (PMD) by PERCIST criteria (Figure 5). The discrepancy of the hypermetabolism area in Figure 5B compared to correct uptake location in Figure 5D and the correct anatomical lesion location in Figure 5A is due to misregistration artefact that can sometimes be encountered in PET/CT imaging.

Moreover, our increased vigilance of these patients with PET/CT demonstrated good overall survival whereby, in this study the rate for best response being stable metabolic disease was 20% and the median survival time after EGFR inhibitor treatment was 17 months. This is comparable to previous studies that demonstrated patients with advanced NSCLC treated with EGFR inhibitors had median survival time of 19.6 months (19). Thus, PET/CT monitoring of EGFR inhibitor targeted therapy is recommended to be incorporated into management algorithms for patients progressing after standard chemotherapy.

Utility of PET/CT has clinical value in prognostication of NSCLC by diagnosing metabolically active disease which can be missed on conventional CT scans. PET/CT is sensitive for early detection of tumour recurrence or disease progression. Therefore, accurate and timely staging and assessment of treatment response can be made for individualised NSCLC treatment. Therefore, we recommend patients who undergo targeted therapy to be followed up with PET/CT imaging for optimization of individualised treatment which and can help tailor chemotherapy treatment accordingly for patients with inoperable NSCLC.

18F-FDG PET/CT is a sensitive imaging modality to detect disease remission or progression in non-small cell lung cancer. Although our study sample is small, it is quite reflective of our population. Nevertheless, we recommend larger sample population and prospective multicentre studies to help better understand altered glucose metabolism in NSCLC and for improved theragnostics.

CONCLUSIONS

Functional imaging utilizing 18F-Fluorodeoxyglucose PET/CT is able to assess metabolic treatment response of non-small cell lung cancers towards epidermal growth factor receptor inhibitor treatment. Application of PET/CT illustrates that proper treatment monitoring with imaging in vivo altered glucose metabolism helps to improve survival and perhaps can determine a suitable time point to modify treatment regime in those who develop resistance.

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