[18]FDG PET/CT and Lung Cancer: Beaconhouse for Treating Oncologists

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Carcinoma of lung is the leading cause of cancers related mortality and comprised of non-small cell lung cancer (NSCLC; 85%) and small cell lung cancer (SCLC; 15%).[1] Over the last few years, significant advancement in molecular profiling and therapeutic strategies like targeted and immunotherapy has resulted in significant improvement in survival in patients with lung cancer.[2] Like other malignancies, precise staging is the most important predictor of survival in lung cancer. Since 2018, 8th edition of Tumour, Node, Metastasis (TNM) staging system has been used for clinical staging of lung cancer which has been approved by the International Association for the Study of Lung Cancer (IASLC) and the American Joint Committee on Cancer (AJCC).[3]

[18]Fluorodeoxyglucose ([18]FDG) positron emission tomography and computerised tomography (PET/CT) is the most commonly used hybrid imaging modality (anatomical plus functional) which has revolutionised the management of various cancers including lung in the last two decades. PET/CT being a hybrid imaging modality has significantly higher diagnostic accuracy. Since most of the tumours are glucose-dependent which has made [18]FDG the most popular metabolic agent with significantly high sensitivity in oncological imaging. However, its specificity is relatively low due to glucose-dependence of various benign conditions like infection and inflammation.

But in such clinical scenarios, CT-based morphological information and clinical history help in improving the specificity. In NSCLC, [18]FDG PET/CT has humongous role in the staging, treatment planning, response assessment, detection of recurrent disease, follow-up and prediction of prognosis in these patients. In this editorial, we will discuss role of [18]FDG PET/CT in staging and response assessment in patients treated with chemotherapy, immunotherapy, and radiation therapy.

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Most of the professional guidelines (such as National Comprehensive Cancer Network, NCCN; European Society of Medical Oncology, ESMO; American College of Radiology, ACR; Society of Nuclear Medicine Molecule Imaging, SNMMI; American College of Chest Physicians, ACCP) recommend [18]FDG PET/CT for staging of patients with NSCLC (Stage I-IV).[4] Published studies have shown that FDG PET/CT in patients with NSCLC resulted in change in TNM staging in 62% and change in management in 52% cases. Published studies have shown that FDG PET/CT in patients with NSCLC resulted in change in TNM staging in 62% and change in management in 52% cases.

[18]FDG PET/CT has a limited role in staging of SCLC as majority have advanced stage time of diagnosis, but in the limited stage disease, it was found to upstage disease in 15%.[4] NCCN guidelines and ACR appropriateness criteria (AC) recommend SCLC staging with ^{18}F-FDG PET/CT in limited-stage disease cases who are considered for curative intent therapy.[5] [18]FDG PET/CT has limited role in certain tumours with lower expression of hexokinase like low-grade adenocarcinoma, colloid carcinoma, mucinous adenocarcinoma, and typical carcinoid. Similarly, pulmonary nodules less than 8 mm tend to show low or no [18]FDG uptake due to partial volume effect, but for lesions >8 mm, it shows high-negative predictive value (NPV) to exclude malignancy.[6]

[18]FDG PET/CT plays a robust role in staging of NSCLC as it has been found to avoid futile surgeries in 1 out of 5 patients.[7] For T-staging, image with the largest tumour dimension in axial, coronal or sagittal plane is selected. [18]FDG PET/CT better delineates viable tumour from the atelectatic lung parenchyma which helps radiation oncologists in excluding that segment from radiation field. In nodal staging, criteria for an abnormal lymph node is >1 cm in short axis (SA) with or without [18]FDG uptake greater than mediastinal blood pool activity. Sensitivity and specificity of [18]FDG PET/CT are significantly higher than contrast-enhanced CT (sensitivity: 75-80% *vs.* 50-70%; specificity: 85-90% *vs.* 65-85%).[8] False positive nodes on [18]FDG PET/CT (>1cm in SA and /or [18]FDG uptake) are not uncommon in infection and inflammatory settings. These false positive nodes pose a diagnostic challenge and NCCN guidelines recommend pathological evaluation for precise nodal staging.[2] About 20-50% of patients with lung cancer have distant metastasis at time of presentation. [18]FDG PET/CT has a sensitivity of 77% and specificity of 95% for distant metastases.[9] [18]FDG PET/CT has ability to show metastasis in normal sized nodes and marrow

deposits which are usually not appreciable on CECT. However, [18]FDG PET/CT has limited sensitivity for detecting brain metastasis due to presence of intense metabolic activity in normal brain cortex.[2] Therefore, MRI brain is considered as an essential step in staging of lung cancer.

Assessment of response to therapy in lung cancer is paramount in the management strategy and treatment outcome. Therefore, precise and early therapeutic response can guide the treating physicians to optimise strategy and mitigate unjustified financial burdens and side-effects. It is a well-known fact that metabolic changes precede anatomical changes in the course of treatment. ^{18}F-FDG PET/CT provides an early and more specific metabolic treatment response assessments preceding anatomic changes in these tumours. This characteristic has allowed [18]FDG PET/CT to grab a front position in therapeutic response assessment.

The most commonly used anatomical response criteria is Response Criteria in Solid Tumour (RECIST 1.1) produced in 2009 which is based on change in size and number of lesions. However, RECIST1.1 limitations are variability in measurement of tumour size and heterogeneity within and among different lesions in the similar patient.[10] Metabolic response assessment to treatment is based on the fact that [18]FDG uptake has direct correlation with viable tumour burden. Therefore, any change in [18]FDG uptake rather than lesion size is a leading indicator of tumour response to treatment. Commonly, change in [18]FDG uptake in PET/CT study is assessed visually (qualitative) and semi-quantitatively using standardised uptake value (SUV). In 1999, the first metabolic response criteria was published by European Organization of Research and Treatment Cancer (EORTC) which recommended to use SUV measured on single pixel having highest [18]FDG uptake (SuV$_{max}$).[11] In 2009, Wahl *et al*. published PET response criteria in solid tumour (PERCIST) which recommended to use SUL$_{peak}$ (i.e. SUL = SUV normalised to body mass index; peak: mean [18]FDG density in 1 cm^3 sphere).[12] Percentage of decline in SuV$_{max}$ two weeks after chemotherapy has been found to predict 5 years survival (60% patient with 60% decrease in SuV$_{max}$; only 5% patients with <25% decline in SuV$_{max}$).[13]

In recent years, immunotherapy (immune checkpoint inhibitors, ICI) as monotherapy or in combination with chemotherapy has become a standard-of-care for patients with advanced NSCLC without actionable mutation. NSCLC shows expression of programmed cell death ligand (PD-L1) in 60%[14] while cytotoxic T-cell associated protien-4 (CTLA-4) is seen in 43-50% cases.[15] ICI has a limited role in SCLC. [18]FDG PET/CT plays an important role in precise response assessment to ICI. Typical response to ICI on [18]FDG PET/CT is profound and durable tumour shrinkage with normalisation or significant reduction in metabolic activity. However, in small percentage of patients, atypical response patterns like pseudoprogression and hyperprogression are seen. Pseudoprogression is defined as transient progression of [18]FDG avid lesions on PET/CT but patient must be clinically stable. This is due to tumour infiltration by patient's T-lymphocytes as an inflammatory response to ICI resulting in enhanced metabolic

activity. However, subsequent [18]FDG PET/CT scan shows a significant metabolic and morphological response. Hyperprogression is defined as two-fold increase in tumour growth with symptomatic deterioration which is likely due to upregulation of immune checkpoints which leads to tumour escape. Due to these atypical responses to ICI, immune-RCEIST (iRECIST) and immune-PERCIST (iPERCIST) criteria have been produced.[16] Compared to the original criteria, iRECIST and iPERCIST have no change for complete response, partial response or stable disease. But progressive disease (PD) has been classified into unconfirmed PD (iUPD) if there is deterioration in [18]FDG avid lesions in clinically-stable patients with an advice to repeat [18]FDG PET/CT after 4-6 weeks. If follow-up [18]FDG PET/CT shows further progression with or without new lesion, this will be considered as confirmed PD (iCPD).

Radiation therapy is considered to be an important member in the armamentarium of NSCLC to be used as curative in small lesions or palliative for the advanced cases. Morphological imaging like CT and MRI play pivotal role in target volume delineation during radiation planning. However, in adjuvant settings like post-surgical and chemo/immunotherapy, delineation of viable tumour volume may become problematic. In such clinical scenarios, [18]FDG PET/CT may help the radiation planning team to use metabolically active tumour volume. Studies have shown that [18]FDG PET/CT based radiation planning has improved local control and mitigated radiation induced toxicity due to irradiation of benign peri-tumoural tissue.[17] There is a general consensus that ^{18}F-FDG PET/CT for response evaluation should be delayed for 12 weeks after completing RT to minimise the risk of false-positive findings.

[18]FDG PET/CT is a powerful hybrid imaging modality playing a synergistic role with advancement in molecular profiling and chemo-immunotherapy in improved survival outcome in lung cancers. Almost all professional guidelines recommend [18]FDG PET/CT in management paradigm of NSCLC. It has a limited role in advanced-stage SCLC but NCCN and ACR-AUC favour its use in staging of limited-stage disease for consideration of curative intent therapy. Its sensitivity and specificity compared with CT is significantly higher for thoracic and extra-thoracic metastasis except brain metastasis due to high [18]FDG uptake in normal brain parenchyma. Since metabolic changes precede anatomical changes, metabolic response criteria (EORTC and PERCIST) are preferred over RECIST 1.1. [18]FDG PET/CT enables oncologist to categorise patient as responder or non-responder with high level of confidence to decide about the future therapeutic strategy. For atypical responses like pseudoprogression and hyperprogression in patients being treated with immuno-therapy, modified immune related anatomical (i-RECIST) and metabolic (i-PERCIST) response criteria have been introduced. These have mitigated unjustified premature discontinuation of immunotherapy in patients with pseudoprogression. [18]FDG PET/CT based metabolic tumour volume assisted radiation planning for curative or palliative intent in patients with lung cancer has been found to have better outcome with relatively low radiation induced side-effects.

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