Positron emission tomography-computed tomography in the management of lung cancer: An update

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Abstract

This communication presents an update on the current role of positron emission tomography-computed tomography (PET-CT) in the various clinical decision-making steps in lung carcinoma. The modality has been reported to be useful in characterizing solitary pulmonary nodules, improving lung cancer staging, especially for the detection of nodal and metastatic site involvement, guiding therapy, monitoring treatment response, and predicting outcome in non-small cell lung carcinoma (NSCLC). Its role has been more extensively evaluated in NSCLC than small cell lung carcinoma (SCLC). Limitations in FDG PET-CT are encountered in cases of tumor histotypes characterized by low glucose uptake (mucinous forms, bronchioalveolar carcinoma, neuroendocrine tumors), in the assessment of brain metastases (high physiologic 18F-FDG uptake in the brain) and in cases presenting with associated inflammation. The future potentials of newer PET tracers beyond FDG are enumerated. An evolving area is PET-guided assessment of targeted therapy (e.g., EGFR and EGFR tyrosine kinase overexpression) in tumors which have significant potential for drug development.

Key words: Lung cancer, PET-CT, staging, restaging, solitary pulmonary nodule

Introduction

The steadily increasing incidence of lung carcinoma makes it an important cause of cancer mortality worldwide in both genders.[1] The second most common cancer (as per statistics in the developed world), it accounts for 12.7% of all new cancer cases and 18.2% of cancer deaths annually and poses a major economic burden on healthcare systems (annually approximately 1,095,000 new cancer cases and 951,000 cancer-related deaths in men and 514,000 new cases and 427,000 deaths in women).[2] The estimated risk is 10-times higher for smokers than non-smokers.[3] Non-small cell lung cancer (NSCLC), the predominant histology with 85-90% of all lung cancers, encompasses three subtypes: Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.[4] The imaging assessment includes morphological imaging such as chest roentgenogram (CXR), CT and the nuclear medicine procedures including PET using 18F-fluorodeoxglucose (FDG), bone scintigraphy and in case of neuroendocrine tumor (NET), somatostatin receptor scintigraphy (SRS). Over the past decade, PET has become a routinely performed procedure for the assessment of lung cancer[5] and can detect abnormalities before they become evident on anatomical imaging.[6] A brief overview of the utility of PET-CT in patients with lung cancer is presented below.

Non-small cell lung cancer

Diagnosis-Solitary pulmonary nodule

A solitary pulmonary nodule (SPN) is defined as a single spherical lesion of 3 cm or less in diameter completely surrounded by lung parenchyma without any associated atelectasis or lymphadenopathy.[7] The probability of lung cancer increases with tumor size, those larger than 3 cm in diameter are frequently malignant.[8] The incidence of malignancy in SPN varies widely (5-70% in the literature), depending upon the patient population studied, geographic location and the prevalence of inflammatory lung disease. Although certain radiological features indicate a benign (calcification) or malignant (spiculated margins) etiology, a reliable characterization is frequently not possible and invasive procedures (e.g., fiberoptic bronchoscopy, transthoracic needle-aspiration biopsy, video assisted thoracoscopy, video-assisted thoracoscopic surgery, or thoracotomy) are employed, all of which are associated with considerable costs and morbidity. Among the various non-invasive modalities,[9,10] CT is considered an excellent tool for detection and localization of SPNs with good sensitivity (96%, range 91-98%) but poor specificity (50%, range 41-58%).[11] FDG-PET is cost effective for evaluation of SPNs in various countries.[12-14] In a meta-analysis, sensitivity and specificity of FDG-PET for SPN diagnosis were 96.8% and 77.8%, respectively.[15] False-negative results occur mostly in association with bronchioalveolar carcinoma, carcinoids, and tumors less than 1 cm in diameter, whereas false-positive findings are frequent because of infectious and inflammatory processes (tuberculosis, sarcoidosis, histoplasmosis, and Wegener’s granulomatosis). Integrated FDG PET-CT has been found to be more useful in characterizing SPN with better sensitivity, specificity, and accuracy [Figure 1].[16]
Semiquantitative analysis of glucose metabolism (SUVmax) is also frequently performed, in addition to visual assessment, because of observer-independence and reproducibility. There have been endeavors to estimate the risk of malignancy by SUVmax of a given nodule and clinically relevant information, with reports that mean SUVmax of malignant SPNs is higher than the benign counterparts (9.7 ± 5.5 vs. 2.6 ± 2.5; P < 0.01). Moreover, all SPNs with SUVmax <1.25 were associated with benign histology. The usual notion is that in patients with an increased surgical risk and a lesion with a low SUVmax, omission of diagnostic thoracotomy may be warranted and the lesion monitored over time. On the contrary, SPNs with a high SUVmax have a high risk of malignancy and therefore require pathological evaluation.

**Staging**

Initial disease staging is important in patients with newly diagnosed NSCLC, to select the most appropriate therapeutic strategy and determine prognosis. It is crucial to correctly differentiate patients with potentially curable disease (who may benefit from radical surgery or chemoradiotherapy) from those who cannot be treated with curative intent and are therefore candidates for palliative therapy. CT, though employed as the imaging modality of choice for NSCLC staging, is being increasingly replaced by FDG PET-CT.

**T-staging**

For the assessment of T stage, the combined PET-CT has increased the accuracy of tumor detection, chest wall, and mediastinal infiltration as compared to PET alone. In one meta-analysis, PET-CT accurately predicted the T stage in 82% of cases compared with 55% and 68% with PET alone and CT alone, respectively. Since diagnostic CT can accurately detect tumor size and infiltration of adjacent structures, use of contrast-enhanced PET-CT is more appropriate in this setting. One potential advantage of PET over conventional imaging is the evaluation of extension of the primary tumor to involve the pleura with a high positive and negative predictive value for the evaluation of malignant pleural effusions. Also FDG-PET is more accurate than CT in determining the size of primary tumor (T1 and T2) when there is adjacent collapse or consolidation.

**N-staging**

Clinical staging of the nodal involvement in NSCLC is classified into four categories: N0, N1, N2, or N3. The identification of nodal involvement is vital to select candidates for curative surgery. Patients with N0–N1 disease (no metastatic lymph nodes or only intrapulmonary/hilar nodes) are generally candidates for surgical resection. On the contrary, patients with N2 disease (ipsilateral mediastinal lymph nodes metastases) could gain benefit from a combination of local and systemic treatment. Patients with N3 disease (contralateral mediastinal lymph nodes metastases) are presently considered unresectable.

Conventional imaging modalities (CT/MRI), using only dimensional criteria (>1 cm) to detect nodal involvement, have poor accuracy in differentiating benign from malignant nodal disease (sensitivity: 60-83%; specificity: 77-82%). In one study, 44% of metastatic lymph nodes in NSCLC measured <1 cm whereas 77% without metastatic lymph nodes had a lymph node measuring >1 cm in the short-axis diameter. FDG PET-CT is reported to have a higher diagnostic accuracy than either CT or PET alone. A recent multicenter study has shown that FDG PET-CT has very high negative predictive value (91%) and specificity (83%), but limited positive predictive value (29%). Similar results were seen in a recent meta-analysis. With respect to nodal size, the sensitivity of FDG PET-CT to detect malignant involvement was 32.4% in nodes <10 mm, and 85.3% in nodes ≥10 mm. It has been suggested that dual-time point imaging can improve the sensitivity of FDG PET-CT for mediastinal nodal staging.

Although FDG-PET/CT appears more useful than other imaging modalities for the assessment of nodal metastatic involvement, PET findings cannot replace histological confirmation of FDG-positive lesions by mediastinoscopy. False-negative rate for micrometastasis detection has been reported to be as high as 8% and false-positive results has been reported in the setting of endemic granulomatous diseases. False-negative rate for micrometastasis detection has been reported to be as high as 8% and false-positive results has been reported in the setting of endemic granulomatous diseases. Thus, FDG PET-CT cannot ovate the need for invasive procedures. However, FDG PET-CT provides valuable information about inaccessible nodal stations that may be missed by conventional imaging. Lymph nodes in the aorto-pulmonary window, anterior mediastinum, and in the posterior subcarinal region are difficult to reach without modifying the mediastinoscopic approach and are not routinely sampled. FDG-PET detection of hypermetabolic lymphnodes at these stations suggests the need for other methods of lymph node evaluation like anterior mediastinotomy/transbronchial or percutaneous biopsy or endoscopic-guided fine needle aspiration. In one prospective study of 61 patients with stage IIIA disease who were candidates for neoadjuvant chemotherapy before being planned for surgical resection, FDG-PET resulted in tumor upstaging in 30% causing a switch to palliative treatment in 19% of patients. PET-CT virtual mediastinoscopy has also been found to be a useful adjunct.
**M-staging**

Approximately 18-36% of patients with newly diagnosed NSCLC have distant metastases at presentation, which has major implications on management and prognosis. The commonest sites for metastatic disease in NSCLC are the brain, bone, liver, and adrenals (in decreasing order) at presentation. Furthermore, among the patients apparently radically treated for NSCLC, around 20% relapse due to the presence of undetected micrometastasis at initial staging. Conventional staging for distant metastasis includes a CT scan of the chest including the upper abdomen for assessment of adrenal glands and liver, while bone scintigraphy and brain imaging are performed only for stage IIIA or IIIB.

Being a whole-body non-invasive technique, FDG PET-CT provides valuable information regarding metastatic spread [Figure 3]. FDG-PET detects clinically unsuspected distant metastases in up to 28% of patients with NSCLC and impacts clinical management in as high as 53% of cases. In one randomized study, FDG-PET reduced futile thoracotomies to 25% (from 46% with conventional work-up alone) in patients with clinical stages I-II tumors and to 11% (from 29% with conventional work-up alone) in patients with clinical stage III tumors. In the ACOSOG Z0050 trial, 6.3% of patients were found to have extracranial distant metastasis not seen on previous CT staging at the time of FDG-PET.

Adrenal masses are detected in up to 20% of patients with NSCLC at initial presentation but approximately two-thirds of those actually represent adenomas, rather than metastases. FDG-PET has shown promising results in differentiating benign from metastatic adrenal masses in patients with known or suspected malignancies. In the study with the largest patient population, Kumar et al. studied the usefulness of FDG-PET in the evaluation of adrenal masses detected on CT/MRI in NSCLC. One hundred thirteen adrenal masses were evaluated in 94 patients and interpreted as positive if FDG uptake of the adrenal mass was greater than or equal to that of the liver. The sensitivity, specificity, and accuracy for detecting metastatic disease were 93%, 90%, and 92%, respectively.

Metastases to the CNS are common and detected in 18% of patients with M1 disease at presentation. FDG-PET is not very useful due to increased FDG activity in normal brain. Bones are a common site of metastasis with an overall prevalence of 20% (range, 8-34%). FDG PET-CT is highly accurate for detection of bone metastasis [Figure 4]. In a recent meta-analysis, it was shown that the pooled sensitivity and specificity for the detection of bone metastasis in lung cancer using FDG PET-CT, FDG-PET, MRI and bone scan were 92%, 87%, 77%, and 86%; and 98%, 94%, 92%, and 88%, respectively. FDG-PET appears more accurate than CT in detecting liver metastases because of its better specificity. In addition to its clinical utility, FDG PET-CT has also been found to be a cost effective staging modality by avoiding futile thoracotomies.

**Treatment planning**

Radiation therapy (RT) is the attempted curative treatment in early stage (I–II) NSCLC patients who are not candidates for surgery. The use of FDG PET has important implications for the radiation oncologist, since PET provides valuable information influencing radiotherapy techniques, target volumes definition and radiation exposure.
Although the definition of volumes on PET images alone might be problematic due to the poorer resolution and higher noise levels; when combined with structural imaging, such as CT, FDG-PET provides the best available information on tumor extent. PET-CT should be used for RT planning in NSCLC because it more accurately images tumor extent than CT alone. The impact of PET on RT planning can be summarized in both a reduction of the dose delivered to normal surrounding tissue (when PET tumor area is smaller than that defined on CT) and in the inclusion of adjacent areas with viable tumor cells outside the radiation fields (when PET detects more extensive tumor area than CT). FDG-PET has been reported to significantly change nodal staging in the thorax, usually by showing more positive nodes than CT, and PET-CT imaging can improve the accuracy of target volume delineation using anatomic biological contour (ABC), determined directly on PET-CT images. In a modeling study, van Der Wel et al. reported that for 21 patients with N2 or N3 NSCLC, the use of PET-CT in radiotherapy planning resulted in a lower level of radiation exposure to the esophagus and lungs, allowing a significant increase in the dose delivered to the tumor. Finally, PET, especially PET-CT imaging has another positive effect on tumor volume delineation: Significantly reduced inter-observer and intra-observer variability for tumor volume delineation.

**Treatment response monitoring**

Innovations in aggressive surgical techniques, neoadjuvant and adjuvant chemoradiotherapy and molecularly targeted therapies have led to spiraling costs and, in some cases, increased morbidity while yielding only modest improvements in survival for patients with NSCLC, particularly early-stage disease. Thus, there is pressing need to validate the effectiveness of treatment in individual as well as in specific groups of NSCLC patients for the purpose of developing appropriate treatment guidelines that would allow the termination of ineffective agents and a change to alternatives that may be more effective.

Molecular imaging offers the potential to characterize the nature of tissues on the basis of their biochemical and biological features [Figure 5]. One of the major theoretical advantages of FDG-PET compared with structural imaging techniques is that there is usually a more rapid change in cellular metabolism than in tumor size. A prospective study by MacManus et al. suggested a much more powerful correlation of outcome to PET metabolic response versus CT response. In another study, quantitative dynamic FDG PET performed 2 weeks after chemoradiotherapy in a cohort of 29 patients with 30 lesions demonstrated a correlation between the residual rate of glucose metabolism, as estimated from FDG kinetics, and the pathological tumor response. A larger retrospective study involving 56 patients, 33 of whom received neoadjuvant chemotherapy and 23 of whom received chemoradiation, revealed a nearly linear correlation between the change in the SUVmax and the percentage of nonviable tumor in the resected material ($r^2 = 0.75$; $P < 0.001$). Similarly, a study evaluating the utility of FDG PET-CT in assessing the response to neoadjuvant chemotherapy/chemoradiotherapy found a significantly greater percentage decrease in the SUVmax in patients showing an excellent pathological response in the primary tumor than in those with greater than 10% residual viable cells ($P = 0.005$). In another study involving patients treated with neoadjuvant chemotherapy, Dooms et al. found that patients with persistent major mediastinal nodal involvement on FDG PET had a 5-year overall survival rate of 0%. Apart from response to chemotherapy and radiotherapy, FDG PET-CT can be used to monitor response to biological therapy. It is superior to CT for this purpose because of the fact that metabolic changes appear earlier than anatomical changes. FDG PET-CT has been shown to be useful in monitoring response to the EGFR kinase inhibitor, erlotinib in few studies.

However, FDG uptake in inflammatory tissues must...
be considered when FDG-PET is used for response assessment after radiotherapy. Serial imaging during and after radiotherapy suggests that inflammatory 18F-FDG uptake in normal tissues increases in the first few months after treatment rather than occurring early during radiotherapy. However, these delayed changes need not prevent an experienced observer from correctly assessing a treatment response visually. Accurate region-of-interest assignment is critical when the SUV is used to assess the response after radiotherapy because uptake in the uninvolved lung may be in the range considered to be malignant (SUV-2.5).

Prognosis
As relatively few patients with locally advanced NSCLC are currently cured, the ability of diagnostic tests to predict the duration of survival is an important measure of therapeutic efficacy and may help in better selection of patients for salvage or palliative therapies. The ability of FDG-PET to provide prognostic information was demonstrated in a pilot study involving 15 patients receiving induction chemotherapy (n = 9) or radiotherapy (n = 6). It was observed that patients with PET down-staging had significantly longer cumulative survival than patients with a persistent mediastinal nodal abnormality (P = 0.014), whereas a partial response on CT was not predictive of outcome. In a larger prospective study, a metabolic response to chemoradiation, as assessed by visual analysis of FDG-PET, was also much more powerfully correlated with survival than the response on CT determined from WHO criteria. Another study involving 70 patients undergoing neoadjuvant chemoradiation found that patients with either a complete metabolic response (CMR) had significantly longer survival than patients with a partial metabolic response (PMR) (P < 0.0001) while progressive disease was associated with unfavorable outcome. Similar promising results of PET response in prognostication of disease have been reported by other investigators as well.

In a systemic review of 13 studies comprising 1474 patients with NSCLC, increasing SUV on FDG PET was found to be prognostic as a continuous variable for lower survival though no clear cut-off was identified. In a recent prospective study with 282 stage I lung cancer patients, it was demonstrated that SUVmax of primary tumor was an independent prognostic factor for survival. Patients with an SUVmax more than 4.7 had a significantly higher risk of recurrence. Similar results were also seen for stage III and IV tumors. There have been important outliers amid all this encouraging data, though, overall it is thought that tumors with high pre-treatment SUVmax on FDG-PET have inferior prognosis. However, there may be differences among disease stages and treatment modalities.

Small cell lung cancer
Clinically, SCLC is more aggressive than NSCLC, presenting with a rapid doubling time and higher propensity for widespread metastatic disease. Overall prognosis is dismal. In fact, despite initial chemosensitivity, most patients with SCLC relapse and die from recurrent disease. At presentation, about 60-70% of patients with SCLC have extensive disease while 30-40% have limited disease (limited disease is defined as disease confined to one hemithorax, the mediastinum, and the supraclavicular lymph nodes). Diagnostic procedures commonly used to stage the disease include chest and abdomen CT, brain CT or MRI, radionuclide bone scans, and bone marrow aspiration.

In comparison to NSCLC, the data on SCLC with PET-CT is limited. The impact of PET on stage classification of newly diagnosed SCLC has been investigated by several authors that reported how PET allowed a modification of stage and clinical management in 10-33% of cases. In a population of 120 SCLC patients studied for staging by PET and conventional imaging, PET upstaged 10 patients and downstaged 3 patients. In another recent study, among the 26 patients with limited disease on conventional imaging, 4/26 (15%) were upstaged to extensive disease after PET while among the 20 patients with extensive disease on conventional imaging, 8/20 (40%) were down staged to limited disease. Because of the high physiological accumulation of FDG in brain, in patients who are found to have limited disease with PET, if brain metastases need to be excluded, a brain MRI is necessary. The potential role of FDG-PET to assess early therapeutic response and disease prognostication have also been demonstrated in a limited number of studies.

Newer directions: Tracers beyond FDG
FDG PET-CT is now an established modality in management of lung cancer. A host of newer radiopharmaceuticals which target different aspects of tumor biology are being explored in lung cancers. These include the proliferation tracer 18F-fluorothymidine which has been evaluated in few studies and found to be useful. Other tracers which provide information regarding hypoxia (18F-FMISO, 64Cu-ATSM), angiogenesis (RGD peptides), amino acid metabolism (11C-Methionine), and choline metabolism (11C-choline, 18F-fluorocholine) have also been evaluated. An evolving area is the non-invasive assessment of epidermal growth factor receptor (EGFR) and EGFR tyrosine kinase overexpression in tumors by PET imaging that has the potential for in vivo a priori determination of EGFR-targeted drug efficacy. These agents might give better insight into tumor behavior, aggressiveness, and therapy-related toxicity, thereby helping in formulation of individualised treatment strategies with targeted agents. However, substantial prospective assessment is needed before these agents come into routine use.

Conclusions
PET-CT has established itself as an important step in the management of patients with lung cancer. FDG PET-CT
PET-CT in lung cancer

is useful for characterising solitary pulmonary nodules. In addition, it has definite role in staging, radiotherapy planning, response monitoring and prognostication of NSCLC. While data for SCLC is limited, still FDG PET-CT appears to be useful in this subgroup. Further evaluation of newer PET tracers in lung cancer will better our understanding of tumor biology and may pave the path for personalised medicine.

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