

Role of positron emission tomography-computed tomography in non-small cell lung cancer

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Abstract

Lung cancer is the leading cause of cancer-related mortality worldwide. Non-small cell carcinoma and small cell carcinoma are the main histological subtypes and constitutes around 85% and 15% of all lung cancer respectively. Multimodality treatment plays a key role in the successful management of lung cancer depending upon the histological subtype, stage of disease, and performance status. Imaging modalities play an important role in the diagnosis and accurate staging of the disease, in assessing the response to neoadjuvant therapy, and in the follow-up of the patients. Last decade has witnessed voluminous upsurge in the use of positron emission tomography-computed tomography (PET-CT); role of PET-CT has widened exponentially in the management of lung cancer. The present article reviews the role of 18-fluoro-deoxyglucose PET-CT in the management of non small cell lung cancer with emphasis on staging of the disease and the assessment of response to neoadjuvant therapy based on available literature.

Key words: Positron emission tomography; Diagnostic imaging; Neoplasm staging; Carcinoma; Non-small-cell lung cancer; Lung neoplasms

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Core tip: The evidence is evolving for the role of positron emission tomography-computed tomography

(PET-CT) in the management of non-small cell lung cancer (NSCLC). Available literature supports the use of PET-CT in the staging of NSCLC to have better disease staging (assessment of mediastinal and extra-thoracic disease). Detection of abnormal mediastinal nodes at various basins is the potential advantage of PET-CT for better targeted biopsy and it may lead to reduction in futile surgical interventions. The role of PET-CT in the prediction and assessment of response to neoadjuvant therapy needs further studies.

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INTRODUCTION

As per GLOBOCAN 2012 data, lung cancer is the leading cause of cancer related death worldwide; an estimated 1.8 million new lung cancer cases occurred in 2012, accounting for about 13% of total cancer diagnoses^[1]. Non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma are the main histological subtypes and constitutes around 85% and 15% of all lung cancer respectively^[2]. Multimodality treatment is the key to successful management of lung cancer depending upon the histological subtype, stage of the disease, and performance status of the patient. Imaging modalities play an important role in the diagnosis and accurate staging of the disease, in assessing the response to the neoadjuvant therapy, and in the follow-up of the patients. The role of positron emission tomography-computed tomography (PET-CT) has widened exponentially during the last decade in the management of solid tumors, and lung cancer is no exception to this trend. In the present article, we review the role of 18-fluoro-deoxyglucose (FDG) PET-CT in the management of NSCLC with emphasis on the staging of the disease and the assessment of the response to neoadjuvant therapy.

ROLE OF FDG PET-CT IN THE STAGING OF LUNG CANCER

Accurate staging is essential in formulating an optimal management plan for the patient, predicting the prognosis of the disease, and to evaluate and compare the results of various clinical studies by providing a uniform staging terminology across the centers. Staging of NSCLC incorporates assessment of primary tumor, regional lymph nodes and distant sites. Being a whole-body imaging technique, PET-CT has proved to be an enticing option to assess the loco-regional extent and distant sites in a single non-invasive examination. Moreover, combination of functional and anatomical imaging in a PET-CT examination provides greater

accuracy in the disease staging.

Primary tumor

A radiologic imaging is required in the assessment of extent of primary tumor. Contrast enhanced computed tomography (CECT) of the chest is traditionally considered the standard imaging modality for delineation of anatomical extent of the primary tumor (Figure 1). At times, magnetic resonance imaging (MRI) is also needed in case of superior sulcus involvement or mediastinal involvement (assessing the relation to heart or great vessels). Because of poor spatial resolution, PET-CT does not offer much advantage over conventional CT/MRI. However, PET-CT has been shown to be superior to CT/MRI in assessing tumor size when there is associated post-obstructive atelectasis or consolidation^[3]. Pawaroo *et al*^[4], in their study of 59 patients of NSCLC, showed that PET was better than CT with either soft-tissue or lung windows in delineating primary NSCLC if surrounding collapse or consolidation is present. They cautioned that PET may not be reliable for assessment of alveolar cell carcinoma owing to low FDG accumulation. This is to be highlighted that accurate primary tumor is useful for radiotherapy planning if consolidation or collapse surrounds the primary tumor.

Another potential advantage of PET-CT over the conventional imaging is its ability to diagnose pleural disease. Though presence of malignant pleural disease confers a M1 disease and precludes curative surgery; post-obstructive pneumonia related benign effusion should not be erroneously diagnosed as malignant. Conventional imaging modalities like CT and MRI are able to detect pleural thickening or nodularity; however, they are limited in their capacity to differentiate malignant from benign growths with a reasonable amount of certainty^[5]. In an analysis of FDG PET-CT images of 33 lung cancer patients with pleural effusion, Kim *et al*^[6] suggested that FDG PET/CT can be used as a reliable and noninvasive method for the differentiation of malignant and benign pleural disease in patients with NSCLC. Similar results were also reported by Gupta *et al*^[7], they reported PET-FDG imaging is a highly accurate and reliable noninvasive test to differentiate malignant from benign pleural effusion and/or pleural involvement in patients with lung cancer (sensitivity, specificity, and accuracy of 88.8%, 94.1% and 91.4% respectively). This is also worth mentioning here that thoracentesis may not prove to be futile in up to 30%-40% cases of malignant pleural effusion^[8]. In malignant pleural effusion, ¹⁸F-FDG PET was found to have a sensitivity of 88.8%, a specificity of 94.1%, a positive predictive value of 94.1%, a negative predictive value 88.8% and an accuracy of 91.4%^[9]. Schaffler *et al*^[10], evaluated the accuracy of fluorine ¹⁸F-FDG PET-CT in differentiation of pleural malignancy and cancer unrelated pleural disease in patients with NSCLC and other pleural abnormalities; they found that sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FDG PET was 100%, 71%, 63%, 100%

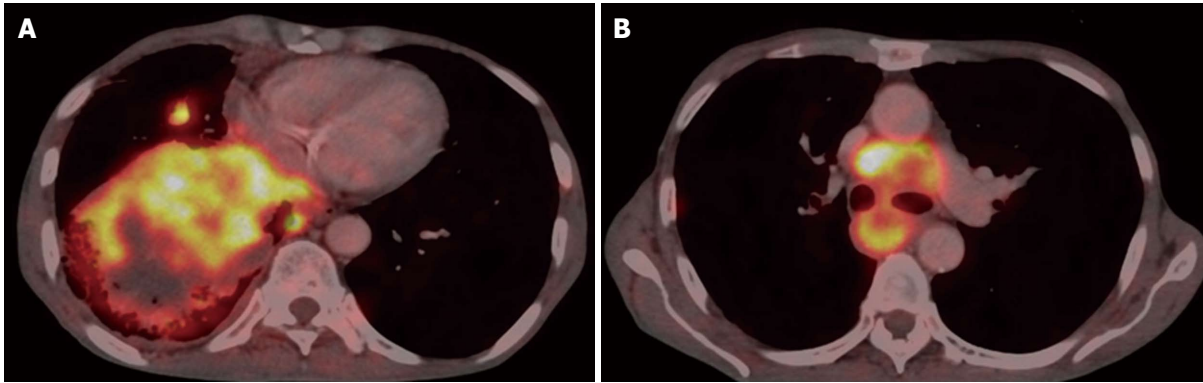


Figure 1 Large soft tissue density mass with heterogeneously increased 18-fluoro-deoxyglucose uptake in the right lung (A) and conglomerated 18-fluoro-deoxyglucose avid paratracheal, subcarinal lymph nodes (B).

and 80%; and those of CT and FDG PET combined, was 100%, 76%, 67%, 100% and 84%. It should, however, be emphasized that all efforts should be made to confirm the metastatic nature of pleural effusion cytologically or by thoracoscopy before committing the patient for a non-curative option.

Regional nodal staging

Undoubtedly, lymph node (N) status is the most important prognostic variable in lung cancer. Accurate mediastinal staging is important to decide optimum management plan for the patient. Presence of mediastinal lymphadenopathy has the potential to change the management approach in NSCLC. CECT determines the nodal staging on the basis of morphological characteristics. Though a number of criteria have been used in various studies to define metastatic node on CT, most widely used criteria is short axis diameter of more than 1 cm on transverse scan^[11]. In a review of three studies including 152 patients total, Toloza *et al.*^[12] concluded that the sensitivity, specificity, positive predictive value and negative predictive value of PET-CT in detecting mediastinal staging ranged from 78% to 93%, 82% to 95%, 83% to 93% and 88% to 95% respectively. They further found that the sensitivity, specificity, PPV and NPV of standard CT in detecting mediastinal staging was 57% (95%CI: 49%-66%), 82% (95%CI: 77%-86%), 56% (range, 26% to 84%) and 83% (range, 63% to 93%) respectively in a pooled analysis of 20 studies with 3438 evaluable patients.

In another study of pathologically proven NSCLC cases who underwent staging using PET/CT and CT from July 2008 to February 2012, Xu *et al.*^[13] concluded that PET-CT confers significantly higher accuracy than CT in nodal staging. Though PET-CT had a low sensitivity and high false-negative rate, it was shown to be more specific and accurate than CT in detecting nodal metastasis; the sensitivity, specificity, positive and negative predictive values, and accuracy of PET/CT for detecting nodal metastasis were 51.5%, 95.8%, 74.3%, 89.3% and 87.3% respectively and the corresponding data by CT were 45.5%, 87.1%, 45.5%, 87.1% and 79.2%, respectively following evaluation of

a total of 528 lymph node stations in 101 patients. In a similar study of pathologically proven NSCLC cases who underwent staging using PET/CT and CT, Shim *et al.*^[14] also concluded that FDG PET-CT was significantly better than stand-alone CT for lung cancer staging and provided enhanced accuracy and specificity in nodal staging; they reported that the sensitivity, specificity, and accuracy of CT were 70% (23 of 33 nodal groups), 69% (248 of 360), and 69% (271 of 393) respectively, whereas those of PET/CT were 85% (28 of 33), 84% (302 of 360), and 84% (330 of 393) for the depiction of malignant nodes.

One of the major advantages of accurate loco-regional staging is to avoid futile thoracotomy. In a study to evaluate the clinical effect of PET-CT on preoperative staging of NSCLC, Fischer *et al.*^[15], concluded that the use of PET-CT reduced both the total number of thoracotomies and the number of futile thoracotomies, though it did not affect overall mortality.

The next natural question comes: Can PET-CT replace invasive mediastinal staging with available evidence? American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines^[11] categorized intrathoracic radiographic abnormalities into four groups based on both primary tumor and mediastinal nodes: Group A - extensive mediastinal infiltration that encircles the vessels and airways, so that the discrete lymph nodes can no longer be discerned or measured; Group B - enlargement of discrete mediastinal nodes that can be measured (> 1 cm in short-axis diameter on transverse CT image); Group C - normal mediastinal nodes determined by CT scan, but with a central tumour (within proximal one-third of hemithorax) or suspected N1 disease (enlarged N1 nodes); Group D - normal mediastinal and hilar nodes and a peripheral tumor (within outer two-thirds of the hemithorax). The ACCP guidelines recommended that radiographic (CT) assessment of the mediastinal stage is usually sufficient without invasive confirmation in group A patients as the radiographic evidence of mediastinal involvement is almost universally considered adequate in these patients. In group B and C patients, invasive staging of the mediastinum is recommended over staging by imaging alone. Invasive staging

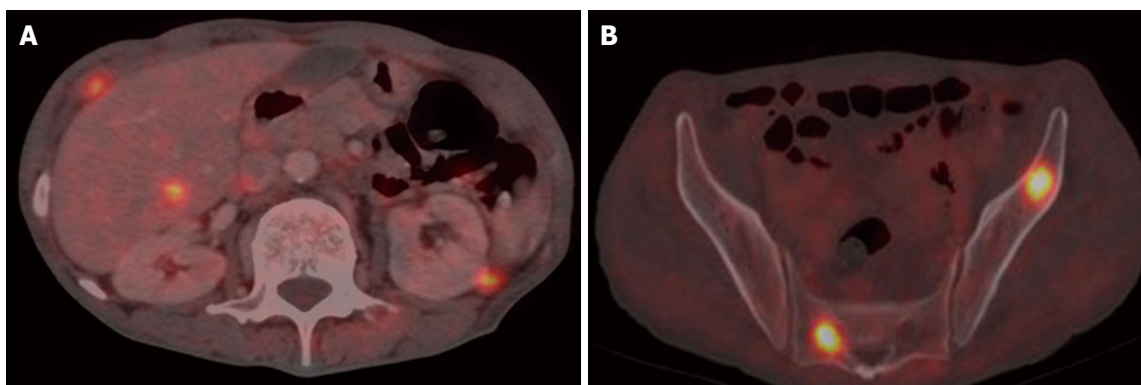


Figure 2 18-fluoro-deoxyglucose avid sub capsular hepatic deposits, liver lesion and left perinephric deposits (A) and 18-fluoro-deoxyglucose avid lesion in the sacrum and left ilium (B).

of mediastinum can be omitted in group D if PET-CT in the mediastinum is negative. The ACCP systematic review further found that the false negative rate of CT in the group of patients with T1 tumours (*i.e.*, clinical stage 1A) is approximately 9% and a negative PET-CT scan in the mediastinum carries an false negative rate of approximately 5% (range, 3% to 6%).

Another important advantage of PET-CT is identification of nodal metastasis sites which are not imaged properly with conventional imaging. Nodal stations at aorto-pulmonary window, anterior mediastinum, and posterior sub-carinal area are difficult to access on conventional imaging; FDG-PET detection of suspected metastatic nodes at these stations mandates may change the strategy of invasive mediastinal staging^[3]. So, the real benefit of PET-CT is to direct the oncologist to nodal stations which need to be targeted.

Distant metastasis

Failure to identify extra-thoracic metastasis is considered as one of the important reason for poor survival in potentially curable NSCLC. This undetected metastasis causes under-staging of disease. Common sites for distant metastasis of NSCLC are brain, adrenal glands, liver, bones, kidney and abdominal lymph nodes (Figure 2).

CT scan of the chest along with upper abdomen is used for scanning the liver and adrenal glands in lung cancer. Adrenal masses are detected in approximately 20% of NSCLC cases at initial presentation. Adenomas, rather than metastasis, are used to be present in two-third of these cases. The per-cutaneous biopsy is the gold standard for confirming the status of adrenal lesions; but it is invasive and difficult to perform. A retrospective study analyzed FDG PET scans of lung cancer patients who were found to have an adrenal mass on CT or MRI scans; the sensitivity, specificity, and accuracy for detecting metastatic disease were found to be 93%, 90% and 92%, respectively following evaluation of 113 adrenal masses (75 unilateral and 19 bilateral; size range, 0.8-4.7 cm) in 94 patients^[16]. The authors concluded that FDG PET was an accurate, noninvasive technique for differentiating benign from

metastatic adrenal lesions detected on CT or MRI in patients with lung cancer. In another study, the depiction of adrenal gland metastasis, the sensitivity, specificity, and accuracy of PET were 74%, 73% and 74%, respectively, whereas those of integrated PET-CT were 80%, 89% and 84% respectively; thus use of PET-CT was more accurate than the use of PET alone for differentiating benign and metastatic adrenal gland lesions in lung cancer patients^[17,18].

Bone scintigraphy is commonly used for detecting bone metastasis in patients with lung cancer. A meta-analysis was performed to evaluate and compare the capability for bone metastasis assessment of PET-CT, PET, MRI and bone scintigraphy in lung cancer patients found that both PET-CT and PET were better imaging methods for diagnosing bone metastasis from lung cancer than MRI and bone scintigraphy; it was concluded that PET-CT has higher diagnostic value (sensitivity, specificity and diagnostic odd ratio) for diagnosing bone metastasis from lung cancer than any other imaging methods^[19].

PET-CT has low sensitivity in detecting brain metastasis due to high physiological glucose uptake by the brain cell. MRI of the brain should be used in patients with neurological symptoms to detect metastasis. FDG PET had shown better specificity in detecting liver metastasis in comparison to CECT^[3].

Table 1 displays the previously published randomized controlled trials (RCTs) to assess the role of PET in the management of NSCLC^[15,20-23]. The first three RCTs incorporated PET while last two RCTs included PET-CT. Three of the five RCTs concluded that use of PET leads to better disease staging which significantly decreases the futile thoracotomies; this has many ramifications including avoidance of non-curative surgery related morbidity and better utilization of health resources.

PREDICTION AND ASSESSMENT OF RESPONSE FOLLOWING NEOADJUVANT THERAPY

Multimodality treatment is the standard of care for stage

Table 1 Previously published randomized controlled trials to assess role of positron emission tomography in non-small cell lung cancer

Ref.	Publication year	Control arm	Test arm	Primary outcome	Result	Conclusion
van Tinteren <i>et al</i> ^[20] (PLUS study)	2002	CI ± brain imaging + invasive diagnostic procedures (n = 96)	CI ± brain imaging + PET + invasive diagnostic procedures (n = 92)	Number of futile thoracotomy	Significant reduction in futile thoracotomy with PET-CT as compared to CI (19 vs 39, P = 0.003, relative reduction 51%, 95%CI: 32%-80%)	Addition of PET to CI prevented unnecessary surgery in one out of five patients in suspected NSCLC
Viney <i>et al</i> ^[22]	2004	CI (n = 92)	CI + PET (n = 91)	Proportions of patients in whom thoracotomy was avoided	No significant reduction in thoracotomy with the use of PET as compared to conventional imaging (4 vs 2, P = 0.2)	PET has the potential for more appropriate stage specific therapy, it may not lead to a significant reduction in the number of thoracotomies avoided
Herder <i>et al</i> ^[23]	2006	CI ± brain imaging + invasive diagnostic procedures (n = 233)	CI ± brain imaging + invasive diagnostic procedures (n = 232)	Number of tests and procedures to finalize staging and operability	Equal mean (standard deviation) number of procedures to finalize staging in CI and PET arm; 7.9 (2.0) vs 7.9 (1.9), P = 0.90	No significant reduction in total numbers of diagnostic procedures in two groups
Fischer <i>et al</i> ^[15]	2009	CI + invasive diagnostic procedures (n = 91)	Conventional imaging + PET-CT + invasive diagnostic procedures (n = 98)	Number of futile thoracotomy	Reduction in futile thoracotomy with PET-CT (21 vs 38, P = 0.05)	PET-CT reduced both the total number of thoracotomies and the number of futile thoracotomies
Maziak <i>et al</i> ^[21]	2009	CI ± brain imaging + invasive diagnostic procedures (n = 167)	PET-CT + brain imaging + invasive diagnostic procedures (n = 170)	Correct upstaging to avoid stage inappropriate surgery	Significantly more upstaging with PET-CT as compared to CI (13.8% vs 6.8%, difference 7.0%, P = 0.046)	PET-CT identifies more patients with mediastinal and extra-thoracic disease than CI

PET-CT: Positron emission tomography-computed tomography; NSCLC: Non-small cell lung cancer.

III NSCLC patients. The therapeutic options available for these patients are definitive chemo-radiotherapy, or neoadjuvant therapy followed by surgical resection. Neoadjuvant therapy includes either chemotherapy or chemo-radiotherapy. Early assessment of response to neoadjuvant therapy is of paramount importance to identify non-responsive tumors; this would help in avoiding continuation of ineffective therapy and would lead to change in treatment strategy early in the course of treatment^[24,25]. PET-CT has been evaluated for its multiple roles in the setting of neoadjuvant treatment; as a predictive marker for response, as a tool of assessment of response, and as a prognostic marker. The basic advantage of PET-CT in response assessment following neoadjuvant therapy is based on the premise that metabolic response precedes the morphological response^[26]. However, there are many grey areas when one considers the role of PET-CT in the neoadjuvant therapy. What constitutes the metabolic response has been a real bone of contentions? What are the valid indicators for metabolic response? How much reduction of standard uptake value (SUV)max should be labeled as response following neoadjuvant therapy? What should be the interval between the pre and post therapy PET-CT. There is limited literature which is marked by the obvious heterogeneity of data: Profile of the patients, stage and histopathological types, type of chemotherapy, use of PET or integrated PET-CT, different PET-CT derived variables, and different end points for comparison. There are a few studies which have assessed the role of

PET-CT in neoadjuvant setting in NSCLC; most studies included patients of both stage III and IV NSCLC.

In a study of 34 NSCLC patients who received neoadjuvant therapy, Cerfolio *et al*^[27] concluded that PET-CT had a significantly high PPV and NPV as compared to CT (81% and 94% vs 50% and 91% respectively for nodal disease); they defined suspicious lymph nodes on FDG-PET scans as any node with a mean SUV of greater than 3.0. Pöttgen *et al*^[28] suggested that corrected SUVmax values from two serial PET-CT scans, before and after three chemotherapy cycles or later, allowed prediction of histopathological response in the primary tumor and mediastinal lymph nodes. In a prospective study of 22 patients with locally advanced NSCLC patients who had pre- and post neoadjuvant treatment PET-CT, Soussan *et al*^[29] concluded that metabolic tumor volume and total lesion glycolysis ratios were the only indices correlated with residual viable tumour after induction chemotherapy; and there was no significant correlation between SUVmax and SUVmean with residual viable tumour. Kaira *et al*^[30] reported that high ratio of SUVmax of the metastatic tumor to the primary tumor (M/P ratio) was associated with a poor response to initial chemotherapy. In a prospective multicenter study of 47 stage IIIA-N2 NSCLC patients who were imaged with PET before the start of platinum-based induction chemotherapy, after the first cycle, and within 3 to 4 wk after completion of the third cycle, Hoekstra *et al*^[31] reported that a 35% decrease of FDG uptake discriminated responders from

non-responders ($P = 0.03$). Prognostic value of PET-CT has also been addressed in the management of NSCLC. In a retrospective evaluation of 205 stage IIIA NSCLC patients who underwent surgical resection after neoadjuvant chemo-radiotherapy, Lee *et al.*^[32] concluded that SUVmax was a sole independent factor for survival in multivariate analysis in whole series (SUVmax cutoff, 13; median survival, 3.0 years vs 4.0 years; $P = 0.016$).

The current review illustrates that there is high heterogeneity in various studies with respect to patient profile, methods of measurement of FDG uptake, timing with respect to anticancer therapy, and different thresholds to define metabolic response; further studies which exclusively include stage III NSCLC patients are required to draw definite conclusions on PET-CT as a tool for neoadjuvant therapy response monitoring.

CONCLUSION

The role of PET-CT in the management of non-small cell lung cancer continues to emerge with time. Besides better loco-regional and distant staging of disease in one sitting, detection of abnormal mediastinal nodes at various basins for better targeted biopsy is the potential advantage of PET-CT and may lead to reduction in futile surgical interventions. This has made PET-CT an essential component in the initial staging of patients with NSCLC. The role of PET-CT in the prediction and assessment of response to neoadjuvant therapy needs further studies.

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