

Original/Research Articles

Role of Whole Body ¹⁸F-FDG PET-CT Scan in Newly Diagnosed Lung Carcinoma Patients for Baseline Staging and Treatment Planning

Atul Marwah*, Sunita Tarsarya*, Ruchira Marwah*, Vinay Ghadge*,
Rajnath Jaiswar*, Pravin Salvi*, Mehjaben*

Abstract

Introduction : We compared the accuracy of staging by whole body coincidence mode ¹⁸F-FDG PET-CT scan with thoracic and abdominal computed tomography scan.

Material and Methods : Histopathologically proven newly diagnosed 109 patients (in 12 months) of lung carcinoma underwent whole body (base of the skull to upper third of thigh) FDG PET scan and baseline thoracic and abdominal CT.

Results : FDG PET changed the N stage in 36 (33%) patients and changed the M stage in 21 (19%) patients. In staging of mediastinal lymphnodes, 23 (21%) patients, which were inoperable by CT had surgically operable disease by PET and 13 (12%) patients who were operable by CT were detected to be inoperable by PET. Ten (9%) patients had metastases demonstrated by PET not found by CT and 11 (10%) patients labelled metastatic by CT did not show metastases by PET. Thus, 34 (31%) patients were downstaged by PET and thereby labelled as potentially operable and 23 (21%) patients were upstaged by PET, these patients received palliative therapies rather than more expensive radical treatments.

Conclusion : ¹⁸F-FDG PET-CT scan plays an important role in baseline staging of lung carcinoma. It substantially influences the treatment planning and is also a cost-effective tool in the overall management of lung carcinoma.

Introduction

Lung carcinoma is the leading cause of cancer related deaths, poses a major burden on clinical oncology.¹ A need exists for an accurate, noninvasive means of staging lung carcinoma that would permit appropriate patient management without the morbidity and cost of surgical staging.² Despite initial evaluation, by morphological imaging, bronchoscopy and biopsy, some patients are found to have unresectable tumour during

surgery or die of recurrent disease within one year of surgery that was intended to cure it.^{3,4} The current noninvasive methods have significant limitations for evaluating the mediastinum and potential extra-thoracic metastases.⁵⁻⁸ FDG PET has found widespread use for in vivo cancer imaging results from the observation of enhanced glycolysis in tumour cells. This phenomenon has been linked to both an increase in the amount of glucose membrane transporters and to an increase in the activity of the principle enzymes controlling the glycolytic pathways.^{9,10} Previous studies have already examined the utility of FDG PET for imaging

*Department of Nuclear Medicine and PET, Bombay Hospital and Medical Research Centre, 12, Marine Lines, Mumbai - 400 020.

the primary tumour, regional lymphnodes and distant metastases and reported the value of PET for staging of lung carcinoma.¹¹⁻¹⁵ The purpose of this study was to assess the clinical impact of wholebody FDG PET, where evaluation is based on qualitative criteria and to compare the accuracy of whole body coincidence mode ¹⁸F-FDG PET-CT scan and baseline thoracic and abdominal CT (conventional imaging). From the clinical and radiologic perspective, one of the most

important decisions is to determine if the patient is a surgical candidate. Using standard TNM staging (Table 1),¹⁶ disease that is stage IIIa or less is potentially resectable, while disease that is stage IIIb or higher is not. Studies have shown that the average 5 year survival (Table 2)¹⁷ in operable cases is significantly higher (40-82%), compared to the inoperable cases who are given palliative radiotherapy/chemo-radiotherapy (< 5%). FDG PET-CT aids in deciding surgically

Table 1 : TNM staging

NSCLC: TNM Staging

Primary tumour	TX	Positive malignant cells; no lesion seen
	T0	No evidence of primary tumour
	TIS	Carcinoma in situ
	T1	< 3 cm in greatest dimension
	T2	> 3 cm in greatest dimension; distal atelectasis
	T3	Extension into the chest wall (including superior sulcus tumours); diaphragm, or mediastinal pleura or pericardium; < 2 cm from carina or total atelectasis
Nodal involvement	T4	Invasion of the mediastinal organs; malignant pleural effusion
	N0	No involvement
	N1	Ipsilateral bronchopulmonary or hilar
	N2	Ipsilateral mediastinal or subcarinal; ipsilateral supraclavicular
Distant metastatic involvement	N3	Contralateral mediastinal, hilar or supraclavicular
	M0	None
	M1	Present

Textbook: PET Basic Science and Clinical Practice. Peter E Valk, Dale L Bailey, David W Townsend and Micheal N Maisey. Edition second, page number 518.

Table 2 : Expected 5 - year survival (with treatment)

Stage	TNM subset	Treatment	Average 5- year survival
Stage IA	T1 N0 M0	Radical surgery ± CT	82%
Stage IB	T2 N0 M0		68%
Stage IIA	T1 N1 M0	Radical RT with platinum based CT	52%
Stage IIB	T2 N1 M0 T3 N0 M0		40%
Stage IIIA	T3 N1 M0 T1 - 3 N2 M0	Palliative RT/CRT	9% - 15%, depending on subset
Stage IIIB	T4 N0 - 2 M0 T1 4 - N3 M0		<5%
Stage IV	Any T, any N, M1		NA

The Washington Manual of Oncology. Ramaswamy Govinda. 2nd edition, page number 137.

operable and inoperable cases significantly altering the treatment as compared to alone.

Material

¹⁸F-FDG coincidence PET whole body scans were performed in our institution for newly diagnosed patients with histopathologically proven lung carcinoma. These were compared with baseline thoracic and abdominal CT scan. For each patient both examinations were completed within one month. Total 109 patients were referred to our department from January, 2008 to January, 2009 were included in the study. There were 80 males (mean age of 63 ± 12 years) and 39 females (mean age of 58 ± 11 years) with a mean age of 60 ± 12 years. All whole body FDG coincidence PET scans were performed using Millenium VG discovery VH Hawkeye dual head coincidence gamma camera. A non-diagnostic CT with a slice thickness of 10 mm, Kv of 140, mA of 2.5, was used for attenuation correction and lesion localization only.

Methods

Patients fasted for minimum of 4 hours with blood glucose levels < 200 mg/dl before intravenous administration of ¹⁸F-FDG injection. Each patient was intravenously injected 9-12 mCi of ¹⁸F-FDG. All patients were made comfortable in a quiet room during 45-60 minutes uptake phase. Whole body FDG coincidence PET scan performed one hour after intravenous administration of FDG. Coincidence PET images obtained were reconstructed in transaxial, coronal and sagittal planes. These images were co registered with non-diagnostic CT images to obtain fusion (anatomical-physiological-PET-CT) images. The extent of the study was from base of the skull to upper third of thigh. Additional brain sections were acquired wherever indicated. A radiologic stage was assigned by using PET and CT imaging independently and were compared.

Data Analysis

PET data was analyzed by qualitative (visual) interpretation. PET and CT images were read independently by two nuclear medicine physicians and a radiologist respectively. A radiologic stage was assigned by using PET and CT imaging independently and were subsequently compared. In case of PET images, the nuclear physicians evaluated the presence or the absence of FDG uptake in the intra and extra-thoracic areas. Lung lesions were considered positive when FDG uptake was greater than mediastinal blood pool activity. Lesions outside the lung were considered abnormal, when FDG uptake was greater than that in the surrounding normal tissue.

Results

Primary tumour evaluation

On the basis of visual interpretation of PET imaging all primary tumours showed an increase in FDG uptake, which was intense in 101 cases and moderate in 8 cases. In our study, histopathological type of tumour did not influence the intensity of FDG uptake.

Evaluation of lymphnodal staging

Results of preoperative mediastinal lymphnodal staging by CT and PET were in agreement in 27 patients. Results of preoperative CT versus PET staging disagreed in 36 (33%) patients for staging mediastinal lymphnodes. PET changed the N stage in 23(21%) patients where it downstaged the nodal disease and labelled the patients operable. In these cases, PET findings were confirmed during surgery. Preoperative nodal staging was in agreement with the PET findings. In 13 (12%) patients who were labelled surgically operable by CT, PET upstaged the disease showing additional N₃ lymphnodes (contralateral hilar/ mediastinal and or supraclavicular), thereby labelling the disease as surgically unresectable disease.

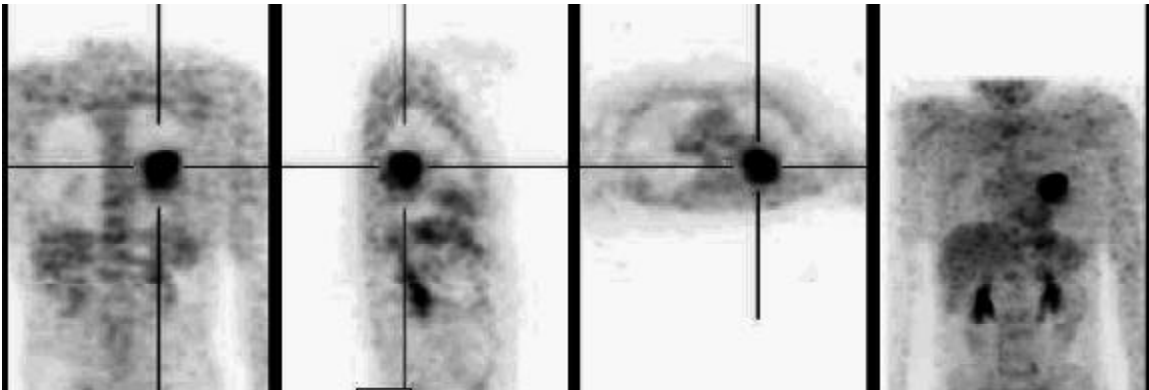


Fig. 1 : Whole body PET scan of 52 year old male, a diagnosed case of adenocarcinoma of left lung. CT revealed primary tumour in the superior segment of left lower lobe and PET scan revealed avidity of tracer at the same site. Thus, for T status evaluation, PET and CT showed agreement in diagnosis of primary lesion.

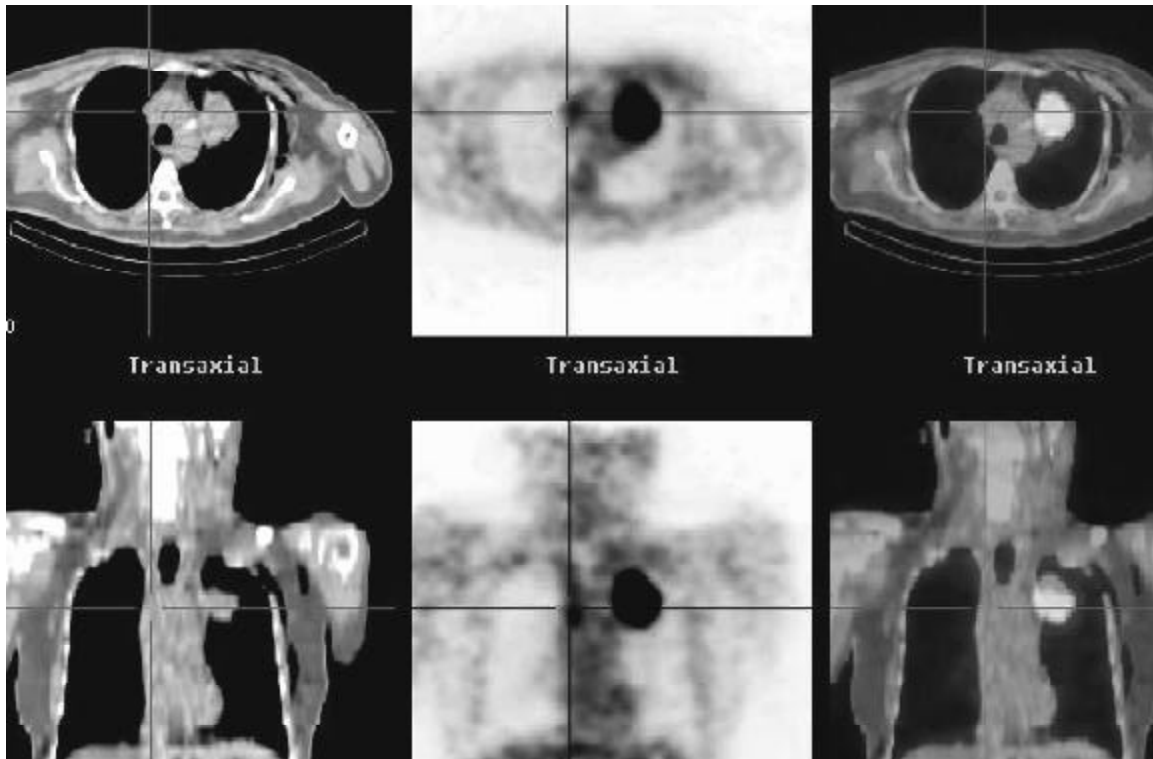


Fig. 2 : PET-CT images of 46 yr old male, a diagnosed case of squamous cell carcinoma of left lung. CT scan revealed primary tumour in the anterior segment of left upper lobe and sub centimeter sized ipsilateral hilar lymphnodes. PET scan revealed activity in the primary tumour and contralateral nodal uptake. Thus, labelled inoperable.

Evaluation of distant metastases

PET versus CT images showed

disagreement in 21(19%) patients. These patients were labelled operable by CT and

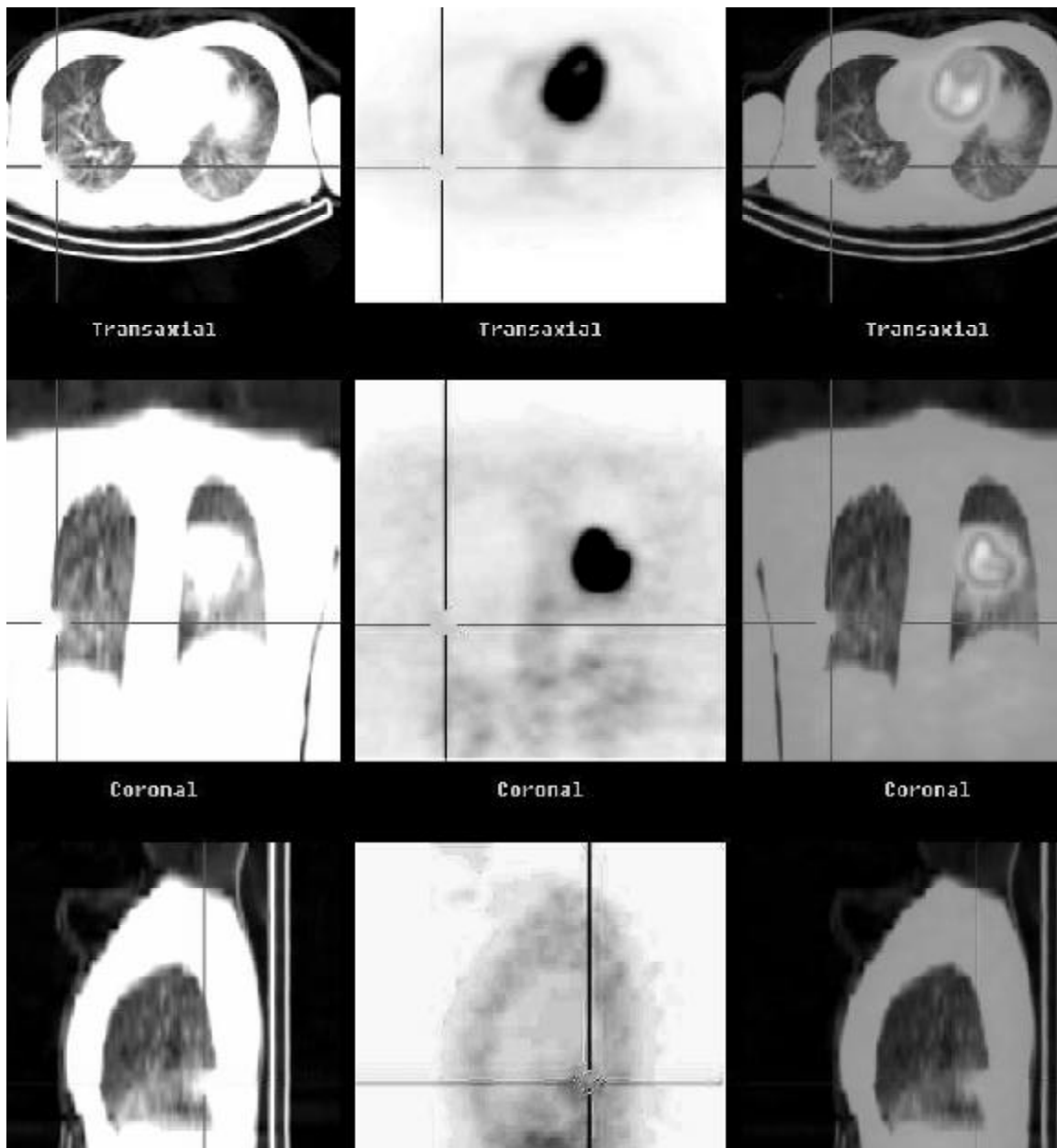


Fig. 3 :PET-CT images of 53yr old male, a diagnosed case of adenocarcinoma of left lung. CT scan revealed primary tumour in the left upper lobe and mediastinal, bilateral hilar, contralateral pre and paratracheal lymphnodes and right subpleural nodule. PET scan revealed activity in the primary tumour in the left lung but revealed no uptake in the right subpleural nodule. Thus, down staged the disease and was labelled operable.

were upstaged by PET which detected additional lesions in bone marrow, adrenal,

liver, different lobe of the same lung or in other lung, making the disease inoperable.

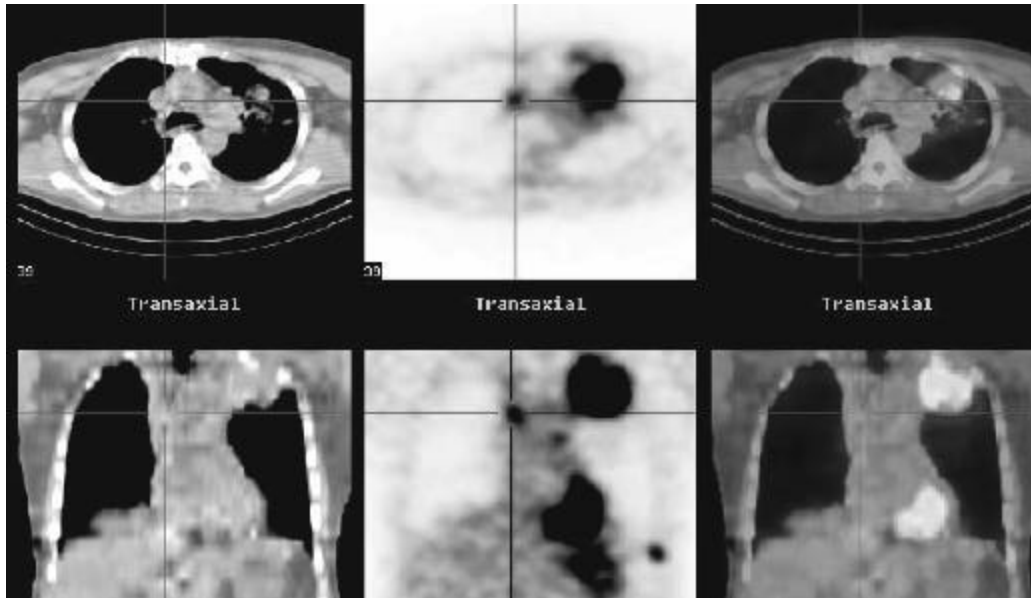


Fig. 4 : PET-CT images of 56 yr old male with histopathologically proven adenocarcinoma of left lung. CT scan revealed primary tumour in the left upper lobe and ipsilateral hilar lymphnode. PET scan revealed activity in the primary tumour in left lung, left hilar and right paratracheal nodal uptake and the left lower lobe subpleural lesion. Uptake in subpleural lesion in the left lower lobe changes the stage to M1 and thus labelled the patient as inoperable.

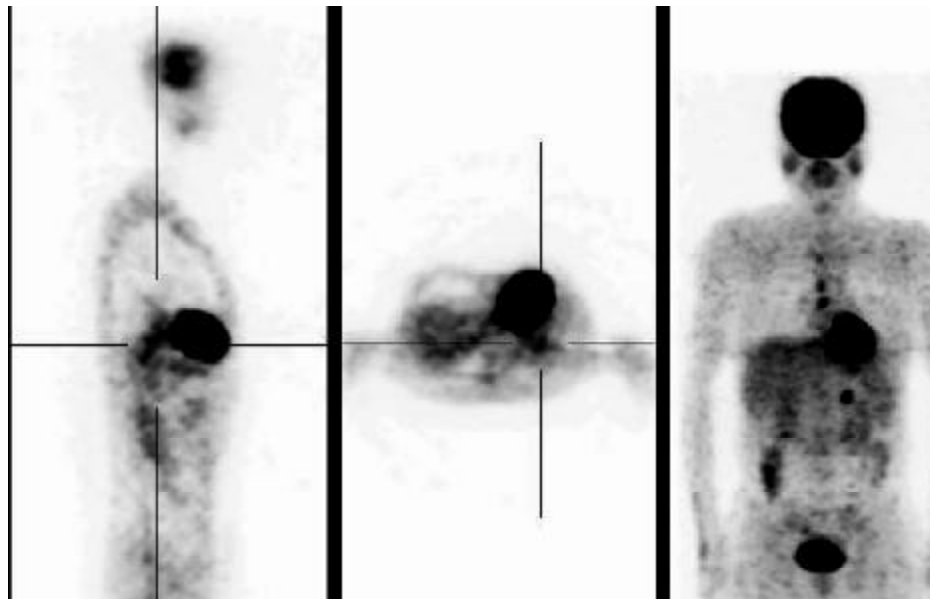


Fig. 5 : Wholebody PET scan of 54 yr old male, a case of adenocarcinoma left lung. CT scan revealed primary tumour in the left upper lobe and no lymphnodes. PET scan revealed activity in the primary tumour in left lung, additional metastatic sites involving the bone, left adrenal and brain thereby up-staged the disease and labelled the patient inoperable.

These patients were subsequently treated by palliative therapy.

Eleven (10%) patients had suspected metastatic disease by CT in the opposite lung nodule or in bulky adrenal. PET clearly demonstrated no FDG avidity in these lesions thereby down staging the disease. These patients availed the chance of better prognosis and longer disease free survival by radical surgical treatment. In this study, 34 (31%) patients were downstaged by PET and thereby labelled as potentially operable, 23 (21%) patients were upstaged by PET, thereby receiving less expensive palliative therapy in place of more expensive radical treatments. All surgically operable cases labelled by PET were confirmed to be correctly staged during surgery.

Discussion

CT provides anatomic and morphologic information; it does not always allow accurate assessment of the extent of disease. PET is used to address some of the diagnostic problems, staging and follow up, because it exploits fundamental biochemical differences between normal and neoplastic cells for imaging purposes.¹⁸

In our study, out of 109 histopathologically proven lung carcinoma cases, fifty five had squamous cell carcinoma, 46 had adenocarcinoma, five had undifferentiated large cell carcinoma and three had adenosquamous carcinoma. None of the patients had histologically bronchoalveolar, carcinoid or mucinous variety which is proven to be low FDG avid, due to their low cellular and low metabolic activity.

In the present study, data was analysed by visual interpretation as various studies have used the same visual analysis and SUVs do not seem to be mandatory in histopathologically proven lung carcinoma

patients. PET and CT imaging showed agreement in tumour (T) status evaluation in all cases. CT and PET are both adequate, and rarely change the T status which did not have a substantial effect on overall stage.¹⁹

FDG PET is a useful tool for differentiating between tumour and peri-tumoral atelectasis and aids in RT planning in lung cancer patients associated with an atelectasis. The information provided by PET results in change in radiation field in 30-40% patients. Appropriate treatment according to the true extent of lung cancer as potentially curable patients who are candidates for radical therapy will have improved treatment planning with reduced risk of geographic miss and less unnecessary irradiation of tissues.²⁰ For solitary pulmonary nodule evaluation, PET has the sensitivity of 93% and specificity of 88%. PET is especially useful in lesions less than 3 centimeter, where biopsy is risky.²¹

For nodal staging, the sensitivity of PET is 96% and that of CT is 79%.²² PET clearly demonstrates an advantage over CT in determining the N status. Patients with metastases to the mediastinal lymphnodes have an average 5 year survival of approximately 10%, compared with the survival rate of 50% in the absence of mediastinal metastases. Patients with negative mediastinal PET can directly go for surgical resection of the primary lesion. Gdeedo *et al* reported, CT had only 63% sensitivity and 57% specificity for mediastinal lymph node metastases, and 24% of normally sized nodes contained metastases.²³ Thoracic CT provides only presumptive, not definitive, evidence for nodal disease. Its current utility is as a road map for guiding lymph node sampling. As small nodes may harbour tumour and large nodes may be reactive.¹⁹

Enlarged lymphnodes visualized at CT, but negative at PET, were proven free of

metastatic involvement with the sensitivity of 92%.²⁴ Recent articles revealed that enlarged lymphnodes in patients with lung cancer are not necessarily metastatic and normal sized nodes may harbour tumour.

WB PET studies demonstrated all lymphnode stations and in some cases obviate mediastinoscopy, as the negative predictive value of PET for N3 disease is 96%. Non enhanced PET CT scan is sufficient for planning surgery in 80% patients.²⁵ Lee and Ginsberg²⁶ demonstrated that 15% of patients with N2-staged lung cancer harboured occult non-palpable supraclavicular disease, which upstaged disease to N3 and resulted in an alteration in treatment. Evaluation of other nodal stations, including prevascular or paraoesophageal stations, requires an additional procedure.²⁷

PET could have a substantial effect on nodal sampling. Whole-body studies demonstrate all lymph node stations and in some cases obviate mediastinoscopy. Because the negative predictive value of PET for N3 disease is identical to that of mediastinoscopy. This is 96%.²³ Patients with negative mediastinal PET findings could go directly to surgical resection of the primary lesion. Patients with a positive PET study in the mediastinum could undergo a single procedure guided by areas of abnormal FDG uptake.^{19,28}

In metastatic evaluation, PET also has an advantage over a combination of other routine studies required to determine the M status. Forty per cent of patients with newly diagnosed lung cancer have distant metastases at presentation.¹ Although clinical and laboratory indicators for metastases are nonspecific, with an accuracy of only approximately 50%.^{29,30} About 40% clinical and laboratory indicators for metastases are nonspecific, with an accuracy of only approximately 50%.^{29,30}

Conventional imaging with thoracic CT, bone scintigraphy, or Brain CT or MR is also less than optimal. PET detects unexpected extra-thoracic metastases in 10-20% of patients and changes therapeutic management in about 20% of patients.

Overall, PET showed greater accuracy than conventional imaging in the detection of distant metastases. In nine patients (9%) not suspected of having metastases at conventional imaging, PET showed metastases. This result is similar to those of other studies.²

When evaluating metastases by site, PET was almost uniformly superior to other conventional imaging modalities. PET was 92% sensitive and 99% specific for bone metastases as compared to bone scintigraphy, with 50% sensitivity and 92% specificity. The whole-body PET study can eliminate the need for staging bone scintigraphy (98% accuracy).¹⁹ In 9% of patients not suspected of having metastases by conventional imaging, PET showed metastases.^{1,2}

For evaluation of adrenal metastases, our findings are in agreement with those of the prior studies, as 6 out of 14 adrenal masses which were indeterminate on conventional imaging were benign.^{32,33} Approximately two-thirds of the adrenal masses detected with conventional imaging in patients with lung cancer are reported to be benign.³³ In a review of 83 adrenal biopsies, Mody *et al*³⁴ reported an 8.4% rate of complications, including pneumothorax, pain, perinephric haemorrhage, intrahepatic haematoma, and hepatic needle-track metastases. The rate of false-negative percutaneous biopsy findings ranges from 2% to 8.6% (35-38). Sensitivity and Specificity of PET for detecting adrenal metastases is 100% and 80-100% respectively, where CT is indeterminate.³⁹

PET has low sensitivity (68%) for brain

metastases. The normal brain has substantial glucose uptake, and a focal area of abnormal accumulation in the brain due to metastases may be difficult to detect with PET. The low sensitivity (68%) is problematic when staging lung carcinoma, as the brain is a common site of metastatic disease and 5.5% - 16.3% of patients with brain metastases are asymptomatic.^{40,41} And PET should not replace conventional imaging for routine staging in the brain.

For evaluation of bone metastases, PET scan when compared with bone scan in detecting bone metastases has high sensitivity and specificity of 99% and 92% respectively, thus whole body PET scan can eliminate the need for staging by bone scan. Radionuclide bone scintigraphy may be eliminated, although brain imaging is still required if clinically indicated.¹⁹

In the study by Edith *et al*, PET proved useful for hepatic metastases, as it showed no false-positive or, to our knowledge, false-negative liver lesions. This is in comparison with eight indeterminate abnormalities at CT. Preliminary study findings have shown PET to be superior to conventional imaging in the detection of liver metastases.⁴²⁻⁴⁶ Whole-body PET examination appears to complement conventional imaging in the liver, particularly when lesions are indeterminate. Whole-body PET examination appears to complement conventional imaging in liver, particularly when lesions are indeterminate.

Patients with locally advanced non small cell lung carcinoma and malignant pleural involvement, a high pleural rather than primary metabolic activity is associated with a particularly dire prognosis.⁴⁷

In this study, PET findings indicated that 23 (21%) patients had disease mistakenly understaged and considered respectable at CT imaging. Thirty four (31%) patients were

considered non-surgical candidates by CT findings, were understaged by PET. In a study by Edith *et al*, PET findings indicated that 12% of patients had disease mistakenly understaged and considered resectable at conventional imaging findings indicated that only 4% of the study patients considered surgical candidates at PET had disease understaged.¹⁹

Sensitivity and specificity of FDG-PET in differentiating benign from malignant lesion have been uniformly high. The ranges in sensitivity, specificity and accuracy are 82-100, 75-100 and 79-99% respectively. The Diagnostic accuracy in lung carcinoma patients by FDG PET is about 92% and that of CT is 75%.⁴⁸

In German meta-analysis, including more than 1000 patients and also evaluating the sensitivity, specificity and accuracy in other metastatic sites, with the same conclusion: high diagnostic efficacy of FDG PET is superior to conventional imaging in lung carcinoma.⁴⁹ For detecting recurrence in lung cancer patients the sensitivity and specificity is 97-100% and 62-100%.

Cost Effectiveness

FDG PET, combining improved patient care with reduced treatment cost, has been found to be decisively more cost-effective than CT.^{50,51} When PET was considered as an addition to conventional staging procedures, the ratio of savings to cost was greater than 2:1. When PET was considered as replacing CT and bone scintigraphy, the ratio was greater than 3:1. PET was effective in reducing management costs even when it was an add-on procedure.⁵¹ Thus, PET is effective in reducing management cost even when it was add on procedure. FDG PET has been approved in US, Germany, UK as a basic and invaluable tool in management of lung carcinoma.⁵²

Conclusion

FDG PET has been consistently proved superior to conventional imaging for staging lung cancer. FDG PET is more accurate than other modalities in differentiating resectable from non-resectable disease. FDG PET in lung carcinoma has the potential to become the most efficient examination in near future for preoperative staging and treatment planning.

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EECP : A NON-INVASIVE THERAPY FOR REFRACTORY ANGINA

Enhanced external counter pulsation (EECP) is a non-invasive, safe and well tolerated therapy, with very few contraindications. It was approved by the FDA in 1995 for the treatment of stable angina, unstable angina, cardiogenic shock and MI and, in 2002, heart failure. The American Heart Association recommends it as a class 11b intervention for treating refractory angina.

The treatment is most often undertaken in an outpatient setting. In the USA, where currently 20,000 patients are treated annually in around 1,000 centres, it is most commonly directed by cardiac interventionists.

The recommended duration of treatment of 35 hours (one to two hours daily for three to seven weeks) is based on the results of pilot studies.

EECP is undoubtedly therapeutic, in the sense that myocardial perfusion has been shown to increase both acutely and in the longer term following treatment.

EECP unlike interventional treatments can be shammed and therefore subjected to randomised controlled trials (RCTs).

This therapy provides augmentation of diastolic flow, through sequential inflation and after-load reduction by simultaneous deflation, from a series of three cuffs applied to calves, lower thigh, upper thigh and buttocks.

The cuffs are inflated to a maximum cuff pressure of 280 mmHg, gated to the ECG and the degree of diastolic augmentation monitored plethysmographically.

Youssef Beaini, Chris Morley, The Practitioner, 2009; 253 : 27-28.