Original Research Article

A prospective study on role of PET-CT in the evaluation of lung masses in a tertiary care center

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Abstract

Background: Lung cancer is a leading cause of death in both men and women worldwide. For the past decades, Computed Tomography (CT) has been the gold standard imaging method in oncology. It has been used for initial staging, tumor evaluation after treatment, and follow-up of patients with cancer. The PET-CT scanners are essentially full ring coincidence detectors, the P.E.T. portion, physically mounted together with CT systems of various types. **AIM:** To study diagnostic role and accuracy of PET-CT in evaluating lung masses in our study population. **Material & Methods: Study Design:** Prospective cross-sectional study **, Study area:** The study was done in the Department of Radiodiagnosis & Dept.of.Nuclear medicine, Yashoda Hospital, Hyderabad. **, Study Period:** 1st Feb. 2011 to 30th June 2011. **, Study population:** patients who were recommended and referred for the evaluation of lung masses detected on chest x-ray or by CT.**, Sample size:** All the patients who were referred for lung masses evaluation, within the study period. **Samplingmethod:** Purpose or convenient sampling method. **Study tools:** The machine used for this study is Siemens biograph sensation 16. **Ethical consideration:** Institutional Ethical committee permission was taken prior to the commencement of the study. **Data collection procedure:** After obtaining institutional Ethical clearance, the purpose of the study was explained to the patients and their consent was taken in this regard. **Observations & Results:** The mean and SD of age of the study population was 61.233 ± 10.101. Out of 30 patients, 10 (33%) patients were females and 20 (67%) patients were males. **Conclusion:** PET CT is sensitive for detecting sub clinical adenopathy and osseous involvement.

Key words: Lung cancer, PET CT, S.U.V. standardized uptake values.

Introduction

Lung cancer is a leading cause of death in both men and women worldwide). About 1.6 million people die of lung cancer each year and the overall 5-year survival rate is only 15%). Most lung cancers are detected at an advanced stage.

During or after the treatment of one cancer, the patient may develop another one, including lung cancer. In patients with synchronous multiple primary lung cancer (MPLC) and contraindications to surgical treatment, the mean survival time is 31 months[1-3] Distinguishing between intrapulmonary metastases and a new primary cancer may be difficult (especially when the tumor histologies are similar).

It may be even more difficult to discriminate between a subsequent primary lung tumor and an intrapulmonary metastatic tumor if the former develops at a location previously treated with radiotherapy, due to the morphological changes that have taken place there. In recent years, the incidence and mortality of lung cancer are always ranked as the highest among all neoplasms. Mass is the principal manifestation of lung cancer, whose diagnosis is of vital clinical significance. Early and accurate diagnosis of lung cancer is critical to its therapy.

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Preventing lung cancer is much more important than screening for it. Randomized clinical trials have shown that obtaining a chest radiograph does not increase the survival of patients diagnosed with lung cancer. Recent studies, however, have demonstrated that annual screening for lung cancer with chest computed tomography (CT) decreases mortality in patients with a history of strong nicotine dependence. For the past decades, Computed Tomography (CT) has been the gold standard imaging method in oncology. It has been used for initial staging, tumor evaluation after treatment, and follow-up of patients with cancer. The method depicts intricate morphological changes with the use of intravascular contrast, abnormal contrast enhancement, and blood flow due to pathological circumstances. However, this conventional imaging technique is not always efficient in the differentiation between benign and malignant lesions. In addition to providing anatomic data, the CT transmission scan can be used to generate an attenuation map that can be used to correct this attenuation effect. Because of the lower photon energy of the CT x-rays (100-140kVp), the CT attenuation coefficients are scaled to reflect the attenuation of the high-energy 511keV emission photons first. Once scaled, they can be applied to the emission data to obtain the attenuation corrected image. This correction process is essential for quantitative assessment (S.U.V. standardized uptake values) as well as improved image quality. Because artifacts can be introduced during this process, any suspected findings can be verified by seeing if the abnormality was present on the uncorrected emission image. If it was present on the uncorrected image as well, than it is likely a true focus of increased uptake.Usually the CT transmission scan is acquired followed by the emission PET scan. Because the scanners

are in the same gantry the patient remains on a single scanning table and in the same position for both parts of the scan. Therefore they are intrinsically registered as seen on the fusion image.

Positron Emission Tomography (PET), on the other hand, is a non-invasive molecular imaging technique that uses various radiolabeled compounds and visualizes metabolic differences between tissues, thus depicting the functional status of a suspicious lesion. PET was developed in the early 1970s and was approved in the United States for limited use in the oncological clinical practice in 1998 [5,6].The development of this method was based on the observation that malignant cells are associated with an increased glycolytic rate and increased cellular glucose uptake. In order to visualize this biochemical procedure, radiolabeled ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is used. FDG is a glucose analogue that has the same cellular uptake as glucose but is metabolically trapped within the cell after enzymatic phosphorylation to FDG-6-phosphate. Therefore, FDG can be used to quantify glucose metabolic rates [7,8]. The PET-CT scanners are essentially full ring coincidence detectors, the P.E.T. portion, physically mounted together with CT systems of various types. The PET tomographs are fitted with various crystals that are used to detect the emission photons and convert them to light signals. This scintillation event is converted to an electric signal that can be displayed on a monitor.

Lung tumors

Lung tumors are mainly divided into Small cell and non small cell tumors.

Histologic Classification of Non-small Cell Lung Cancer

- Squamous cell (epidermoid) carcinoma
- Adenocarcinoma

a. acinar
b. papillary
c. bronchoalveolar
d. solid tumor with mucin
(b) Large cell carcinoma
giant cell
a. clear cell
Adenosquamous carcinoma
Undifferentiated carcinoma

The major distinction in terms of both staging and therapy is between small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

FDG Uptake in Lung Cancer

Lung cancer is very FDG-avid. This uptake becomes even more conspicuous as there is relatively low uptake in the surrounding aerated lung as opposed to other soft tissues. Non-aerated lung may have about three times the activity of aerated lung. As lung tissue is less "dense", an area of atelectasis would have relatively higher uptake per volume of tissue compared to surrounding normal lung. This would hold true for a lung nodule as well. Therefore nodules should not be compared to surrounding aerated lung, but rather to other solid soft tissue to assess for relatively increased uptake. Comparison typically can be made with mediastinal soft tissues or blood pool.

Possible false negatives on FDG-PET

1. Histologic types of lung cancer with variable uptake

- **Pulmonary carcinoid**

a. Atypical carcinoid tumors are more likely to be FDG-avid than typical carcinoid tumors

- **Bronchioloaveolar cell cancer**

a. Solid components of BAC on CT are more likely to be FDG-avid.

2. Necrosis

- An area of necrosis within a tumor will show little FDG activity
- Typically there is an FDG-avid rim however, which can be easily detected.
- Can help direct area of tumor to biopsy
- Directing a biopsy to the most FDG-avid portion of the lesion may improve the diagnostic yield and avoid a false positive biopsy result

3. Size

- Less than 8 mm
- 95% sensitivity > 8mm
- Limited resolution of PET scanner
- Unreliable evaluation due to partial voluming "dilution" effect on degree of uptake

4. Other lesions

- Granulomatous disease is a common cause of false positive single pulmonary nodule.
- Fungal granulomas due to coccidiomycosis, histoplasmosis, and aspergillosis are particularly in endemic areas.
- Granulomas due to tuberculosis.
- Sarcoidosis often has a characteristic pattern, but it can cause false positives.
- Active infections
- Post infectious nodules

SUV Criteria

Standardized Uptake Value takes into account the differences between normalizing for body weight, for lean body mass, or for surface area.

SUV calculation

SUV = [mCi/ml (decay corrected) in tissue] / [mCi of tracer injected/body weight (grams)]

- "Cut off" value between benign and malignant single pulmonary nodules is in the range 2.0-2.5.
- Value decreases for smaller lesions due to partial volume effects
- Indirect comparison can be made to the mediastinal blood pool (generally in the range of 2.5).
- A positive nodule will demonstrate uptake greater than the mediastinal blood pool.
- Using this internal control can help avoid errors in the SUV calculation
- Quantified SUV facilitates comparison with the mediastinal blood pool on the display

Advantages of FDG-PET in Lymph Node Staging

- FDG-PET has the ability to identify positive nodes that are smaller than the standard CT pathologic enlargement criteria of one centimeter as well as identify larger size nodes that are negative.
- PET imaging with anatomically fused images is advantageous in being able to identify the exact location of mediastinal nodes near the midline.

Staging - Distant metastases

- One of the most important roles for FDG-PET
- Commons sites

adrenal glands, liver, bones

Stage IV - palliative chemotherapy is indicated.

Direct biopsy site to confirm the highest stage of disease expediting the work up

FDG-PET scan can reveal a distant site of disease that can be biopsied. This often can obviate the need to biopsy the primary lesion. Biopsy based on an FDG-PET scan can make the diagnostic workup more effective.

With this background, the study was undertaken to study the diagnostic role of PET/CT in evaluating the lung masses, in our study population.

Aim

To study diagnostic role and accuracy of PET-CT in evaluating lung masses in our study population.

Material & methods

Study Design

Prospective cross-sectional study

Study area

The study was done in the Department of Radiodiagnosis & Dept.of.Nuclear medicine, Yashoda Hospital, Hyderabad.

Study Period

1st Feb. 2011 to 30th June 2011.

Study population

patients who were recommended and referred for the evaluation of lung masses detected on chest x-ray or by CT.

Sample size

All the patients who were referred for lung masses evaluation, within the study period.

Sampling method

Purpose or convenient sampling method.

Inclusion criteria

All patients with a nodule/ mass lesion in lung parenchyma on chest radiography or CT scan.

Exclusion criteria

1. All pregnant patients
2. Patients with abnormal glucose levels on the day of test.
3. Breast feeding mothers.

Study tools

The machine used for this study is Siemens biograph sensation 16.

Ethical consideration

Institutional Ethical committee permission was taken prior to the commencement of the study.

Data collection procedure

After obtaining institutional Ethical clearance, the purpose of the study was explained to the patients and their consent was taken in this regard.

Patient preparation

Patients were fasted for at least 6 hours before PET/CT examination. Patients blood glucose level was monitored on the day of test and after ensuring a normal level, they were given 2 mci/kg of 18F- FDG. Patients were rested for approximately 50–60 minutes before undergoing a PET/CT scan.

Imaging acquisition

Image acquisition is performed using an integrated PET/CT device (Siemens Biograph Sensation 16). CT was performed from the head to the pelvic floor using a standardized protocol (120 KV, 80 mA with a slice thickness of 5 mm). PET images in early display were acquired using 3D mode for the same scanning range as CT. The acquisition time for PET was 3 minutes per bed position and 5-6 continuous positions were scanned. Delayed images of chest were acquired at 2 hours after injection of 18F-FDG. PET images datasets were reconstructed iteratively using an ordered subset expectation maximization algorithm and were corrected with measured attenuation correction. The SUVmax of the selected ROI in lesions were calculated. CT, PET, and PET/CT infusion images of axial, sagittal and coronal images were obtained through a post processing procedure facility. Radiochemical purity (>95%) of 18F-FDG was verified by analytical HPLC.

Data analysis

Image interpretation of the scntigraphy characteristics of the lesion included not only the SUV max but also the pattern of activity (focal/diffuse), presence of photopenia s/o necrosis. FDG activity in the margins of lesion(sharp margins/smeared out), CT characteristics of the lesion corresponding to the areas of abnormal tracer concentration, presence of additional lesions such as lymphnodal activity , soft tissue or skeletal lesions. In few of the cases a 2hr delayed imaging findings also taken into consideration, lesions with an increase in SUV value after 2hrs are considered as malignant. The cut off value in characterization of lesions as malignant vs benign was taken as 2.5. We tried to characterize the nature of lung masses in unknown cases taking SUV max cut off as 2.5,SUV max < 2.5 as benign and >2.5 as malignant.

Statistical Analysis

The collected data was entered in Microsoft excel 2007 and analysed using SPSS version 20 software, trial version. Data was described in terms of mean ± standard deviation, frequencies as appropriate. Chi-square and t-test will be used to find out the associated significance wherever applicable. The results were presented in the form of charts, graphs, etc. The statistical significance level was fixed at $P < 0.05$.

Observations & results

A total of 30 patients were included and evaluated observing the inclusion and exclusion criteria and following full written consent by patients. Out of 30 patients, 10 (33%) patients were females and 20 (67%) patients were males. The age of the study subjects ranged between 33 years to 81 years. The mean and SD of age of the study population was 61.233 ± 10.101.

Table 1: History of previous malignancy in the study population

Out of 30 subjects, 17 (56.66%) subjects had no previous malignancy where 13 (43.4%) subjects had past history of diagnosis of malignancy. Out of 13 following table reveal the details of previous malignancies,

Carcinoma breast	3(23.07%)
Renal cell carcinoma	2(15.38%)
Post cricoid carcinoma	1(7.69%)
Carcinoma pyriform fossa	1(7.69%)
Gastrointestinal malignancy	2(15.38%)
Mantle cell lymphoma	1(7.69%)
Hodgkins lymphoma	1(7.69%)
Carcinoma lung post treatment	1(7.69%)
Known cystic adenocarcinoma left maxilla	1(7.69%)
TOTAL	**13(100%)**

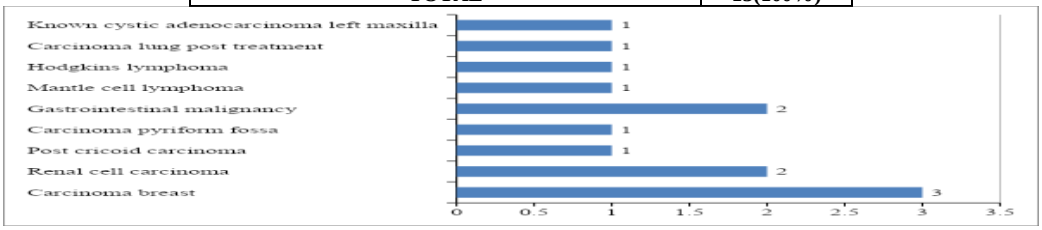

Fig 1: History of previous malignancy in the study population

Of the 30 subjects, 11(36.6%) had solitary pulmonary nodule and rest of the 19(63.4%) had multiple nodules.

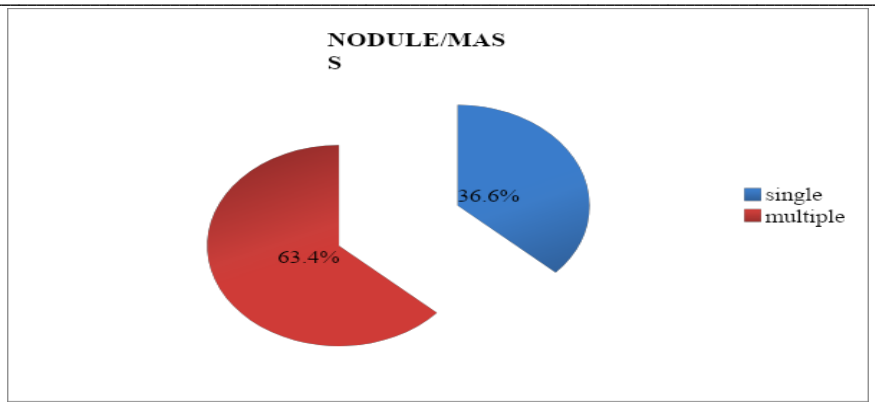

Fig 2: Distribution of solitary and multiple nodules in the study population

Mean size of the lesion was 2.7, largest was measuring 10 cm and the smallest was measuring 0.5 cm. Out Of 30 subjects 18 had spiculated lesions and rest had smooth marginated lesions. Out Of 30 subjects 11 had necrotic lung parenchymal lesions. Out Of 30 subjects, 28 had lung prenchymal nodule/ mass which showed abnormal tracer activity(ATA). Rest of the 2 subjects had lung parenchymal nodule/mass lesion which did not show any abnormal tracer activity.

- Mean value of the SUV max for the lung parenchymal lesions was 8.28.
- Maximum suv max value is 31.4.
- Photopenic areas s/o necrosis are seen in the parenchymal lesion in 11 subjects.
- We tried to characterize the nature of lung masses in unknown cases taking SUV max cut off as 2.5, < 2.5 as benign and >2.5 as malignant.
- Out of the 17 subjects with unknown malignancy, 14 subjects had lung nodules with SUV max >2.5.

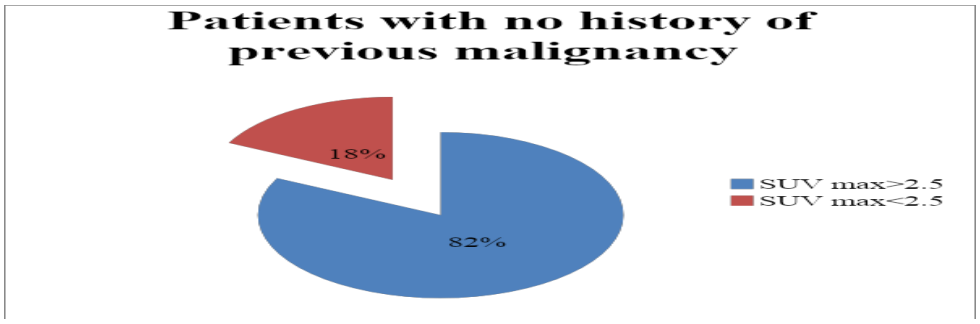

Fig 3: SUV max values in the study population

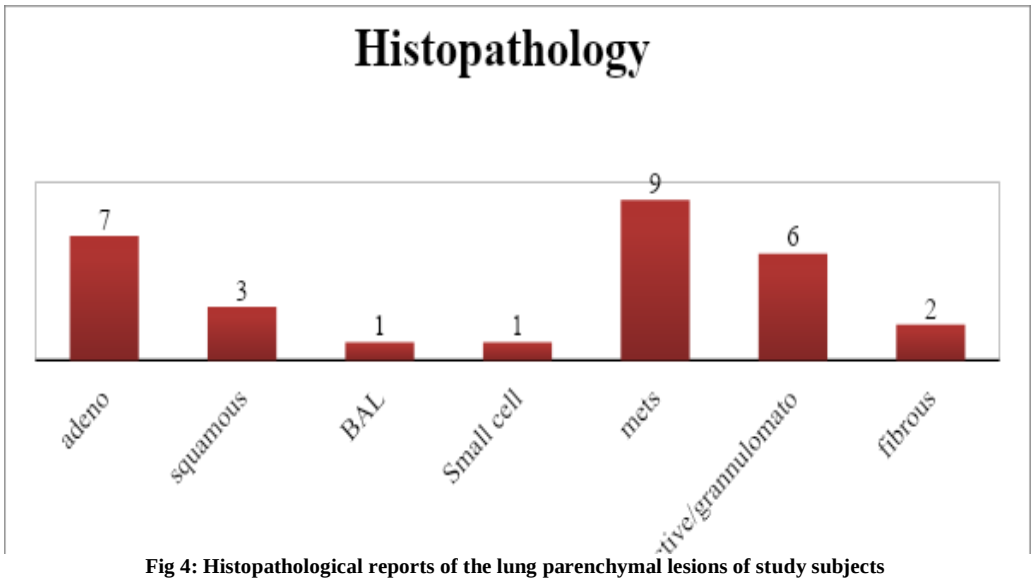

Fig 4: Histopathological reports of the lung parenchymal lesions of study subjects

Out Of the 14 subjects in whom suv max was >2.5, in 12 subjects the lesions turned out to be primary lung carcinomas. And in two subjects the lesion turned out to be metastatic lung nodule, one with primary in the breast and other with primary in the prostate which also showed intense tracer uptake. One case with lung lesion with SUV max of 1.67 turned out to be Bronchoalveolar carcinoma on HPE.

Diagnostic accuracy

- In our study the sensitivity and specificity in characterizing lesion as malignant taking suv max of 2.5 as cut off is 92.8% and 66.67%.
- 7 Of the 13 subjects with history of known primary, showed intense tracer uptake in PET and turned out to be metastatic on HPE.
- In the other 6 subjects, in 4 subjects the lesions turned out to be grannulomatous and in the other two they turned out to be fibrosis on HPE.
- The sensitivity and specificity PET- CT evaluating metastatic lung lesions taking SUV max value of 2.5 as cut off are 100% and 83.3%.
- All the parenchymal lesions which turned out to be adenocarcinoma on HPE showed abnormal tracer activity.
- The man SUV max for adeno carcinomas is 13.58.
- All Parenchymal lesions which turned out be squamous cell carcinoma on HPE showed abnormal tracer activity.
- The mean SUV max for squamous cell carcinoma is 8.36.
- One parenchymal lesion which turned out to be small carcinoma showed abnormal tracer activity. The SUV max for this is 15.20.
- The lesions which turned out to infective or inflammatory grannulomas on HPE also showed abnormal tracer activity. The mean suv max for this lesions is 1.67.

HPE type	Mean SUV max
Adeno carcinoma	13.58
Squamous cell carcinoma	8.36
Small cell carcinoma	15.20
Broncho alveolar carcinoma	1.3
Metastases	7.89
Infective/inflammatory grannuloma	1.67

- Adrenal metastasis was detected in one case.
- In one case adrenal nodule was detected in CT, PET component did not show any uptake we labeled the nodule as benign.
- In one case where the CT did not suggest any bone metastasis, the PET component showed increased uptake in pelvic bones and D11 and L5 vertebral body.

Discussion

The hybrid machine Pet - Ct is a useful investigation in the evaluation and staging of lung lesions. Combined PET and CT adds an incremental clinical benefit by simultaneously depicting both functional and morphological characteristics. Our study consisted of 30 patients (which included 13 patients of known malignancy) in whom lung nodules /mass was detected on X ray/CT. In our study we used a SUV max of 2.5 as a threshold value for characterizing the lesion, lesions with SUV max > 2.5were considered as malignant and lesions with SUV max ,2.5 as benign similar to a study done by orino k etal in showing efficacy of F-18 fluoro deoxy glucose PET scans in characterization of pulmonary nodules.[5-10]

In our study the sensitivity and specificity in characterizing lesion as malignant taking suv max of 2.5 as cut off is 92.8% and 66.67%. Computed tomography and ^{18}F-FDG-PET/CT result in a reduction of radiological artifacts due to cardiac and respiratory movements with a detection rate between 1 and 5 mm. Moreover, the latter positively contributes to the identification of sub-centimeter pulmonary neoplasms because their low necrotic areas favor the SUV and thus overall specificity. According to 2015 BTS Guidelines for the investigation and management of pulmonary nodules, PET-CT has shown a sensitivity of 93.9% and specificity of 88.5% for determining malignancy. Our study was in agreement with these guidelines.

However, a qualitative assessment to define FDG uptake should be advocated by determining the mediastinal blood pool as a baseline threshold [(9)]. Ultimately, these guidelines emphasize the importance of a revision of the uptake cut-off, towards a qualitative dual-time assay rather the absolute SUV value. However, the high sensitivity has to be referred to a pooled cohort of patients with an adjusted stratified risk stratified according to a predefined model (Brock's or Herder's ones), and then, although it would be in conflict with those reported in the general analysis from ACCP [(10)] in a reduction of the occurrences of false positives (e.g. inflammatory diseases) and false negatives (e.g. lepidic adenocarcinoma), stratified rates of occurrence are in agreement with those published in other large series.

Yi et al.[11] evaluated 119 SPNs patients with diameters between 6.2 and 30 mm who underwent both helical dynamic computed tomography (HDCT) and 18F-FDG-PET/CT. Cut-off malignancy index were an enhancement ≥25 Hounsfield Units (HU) for the previous and a SUVmax≥3.5 for the latter. Sensitivity, specificity, diagnostic accuracy, PPV and NPV were 81 versus 96%, 93 versus 88%, 85 versus 93%, 96 versus 94% and 71 versus 92%, respectively. Authors concluded that -FDG-PET/CT can be used as a first level diagnostic investigation (i.e. first-line evaluation tool) but HDCT remains a viable alternative according to its high specificity and acceptable diagnostic accuracy. Kagna et al.[12] retrospectively analyzed 307 SPN patients, of whom 93 at high risk for lung cancer, comparing visual 18F-FDG-PET-low-dose chest CT (LDCT), semi-quantitative 18F-FDG-PET/LDCT and LDCT. Thirty-eight percent of patients highlighted a histological diagnosis of malignancy. Visual PET/LDCT analysis displayed sensitivity of 94%, specificity of 70%, accuracy of 80%, a PPV of 66%, and NPV of 95% compared to 77, 83, 81, 73 and 86% for semi-quantitative PET/LDCT and 97, 48, 66, 53 and 96% for LDCT respectively. Harders et al.[13]reported 168 patients with SPN ≤30 mm in order to verify multi-detector computed tomography (MDCT) and integrated PET clinical reliability in the detection of malignant lung lesions. 18F-FDG-PET/LDCT and MDCT showed a sensitivity of 97 versus 93%, a specificity of 47 versus 53%, a diagnostic accuracy of 81 versus 82%, a PPV of 89 versus 89% and a NPV of 79 versus 63%, respectively. Results seem to be slight in contrast with previous reports, especially in diagnostic accuracy and sensitivity.

In our study, 13 subjects with history of known primary using a SUV max of .2.5,out of 8 subjects 7 were proven to be metastatic and one as Kochs on Histopathology, having an sensitivity and specificity of 100% and 83.3% respectively. Our study showed 100% sensitivity in picking up of mediastinal nodes independent of the size of the nodes (even sub centimeter nodes). In our study PET CT shows 100% sensitivity in picking up adrenal metastasis. One case of Bronchoalveolar carcinoma showed low SUV max and turned to be the only false negative case in our study.

In one case PET CT was able to show abnormal tracer activity in pelvic bones and D11 and L5 vertebral bodies likely to be metastasis which were not picked up on CT. In two cases with extensive necrosis, we are able to guide the site of biopsy by showing areas of

intense uptake and the HPE turned out be positive. In our study we found that males are more affected than females. Non-small cell carcinoma was the most common primary malignancy of lung in our study and in that adeno carcinoma was more common.Dabrowska et al.[14] reported 71 SPN patients with diameter between 8 and 30 mm. Radiological assessment was carried out by contrast-enhancement (CE) CT (enhancement cut-off of 19 HU) and 18F-FDG-PET/CT (SUVmax cut-off of 2.5), in order to assess the accuracy of the two radiological methods in characterizing benign or malignant lesion. Sensitivity was 100 versus 77%, specificity 37 versus 92%, diagnostic accuracy 0.58 versus 0.9, PPV 32 versus 83% and NPV 100 versus 89%. According to sensitivity and NPVs, the authors concluded that CECT should be preferred in low risk patients, while PET should be recommended in high-risk ones due to high specificity and PPV levels. Travis et al.[15] in conclusion of the 2004 International Association for the Study of Lung Cancer/American Society of Clinical Oncology consensus workshop, notified that sub-solid nodules can be an expression of hyperplasia areas and atypical adenomatous hyperplasia (AAH). This latter was found in NSCLC patients with an incidence rate from 10 to 23% [(16)]. However, the presence of a sub-solid pulmonary nodule is often associated with bronchioloalveolar carcinoma (BAC), characterized by a lepidic growth-model along the inter-alveolar septa in absence of stromal invasion. Results were confident with Goudarzi et al. ones[17] The Authors, after an evaluation of 53 patients, underlined absence of a diagnostic role of PET/CT in the T-parameter staging process due to the low radiopharmaceutical uptake. In fact, in only 24% of lepidic or papillary adenocarcinomas, a significant and identifiable metabolic rate was detected; results which are inferior to other primitive tumor uptake values[18-20]

Conclusion

In our study PET CT has a sensitivity and specificity of 92.8% and 66.7% respectively in characterizing the nature of lung nodules/ masses with respect to histopathology. PET CT has a sensitivity and specificity of 100% and 83% respectively in characterizing nodules/ masses detected in patients with pre-existing malignancy. PET CT is sensitive for detecting sub clinical adenopathy and osseous involvement. Although ^{18}F-FDG-PET/CT is the most sensitive non-invasive diagnostic procedure for prediction of malignancy of <10 mm-solid solitary pulmonary nodules, CT alone cannot be considered superfluous due to its characteristics and peculiarities for a proper evaluation of these lesions.

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