

## PET CT Role in Detection of Pulmonary Nodules in Patients with Known Primary Tumor

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### Abstract

**Background:** A lung nodule is defined as an approximately rounded opacity more or less well-defined measuring up to 3 cm in diameter. Lung nodules have broad differential diagnosis including neoplastic process, inflammatory conditions, congenital diseases, etc. Metastatic lung nodules are among the important differential diagnoses of pulmonary nodules as the lungs are the second most frequent site of metastases. Pulmonary metastases indicate disseminated disease and place the patient in stage IV in TNM staging systems which alters the management plan. Conventional radiological methods can provide detailed information about their morphology such as size, location, tissue characterization only. Modalities such as CT or MRI could not distinguish between benign and malignant tumors accurately. 18-fluorine fluorodeoxyglucose (F-18 FDG) positron emission tomography-computed tomography (PET/CT) can play an important role in the differential diagnosis of benign and malignant lung nodules detected during follow-up.

**Aim of Study:** The aim of this study is to investigate the potential of PET-CT to characterize malignant & benign pulmonary nodules using their standardized uptake value (SUV max) as a measurable unit and size of nodules depending on radiological follow-up and clinical assessment.

#### Patients and Methods:

- Those patients were referred to the Radio diagnosis & nuclear medicine departments in el kasr aini Cairo University and private center for PET CT of the chest over a period of 6 month from July 2021 to January 2022.
- This study included 80 patients with positive history of known primary tumor, underwent follow-up study (over period of 6 months) for the most active nodules which are 113 pulmonary nodules (20 solitary, 93 multiple).

**Results:** We retrospectively evaluated pulmonary nodules in 80 patients with positive history of known primary tumor and follow-up to the most active ones which are 113 pulmonary

nodules (20 solitary, 93 multiple). The prevalence of malignancy of pulmonary nodules in oncological patients was 61/80 (76.2%) with PET/CT provided sensitivity 93.4%, specificity 94.7%. ROC analysis revealed SUVmax cut-off  $\approx 1.475$  with significant  $p$ -value  $<0.001$ .

Malignant nodules at follow-up have Mean SUVmax  $8.34 \pm 6.76$ , while benign nodules at follow-up have Mean SUVmax,  $0.58 \pm 0.99$  with significant  $p$ -value  $<0.001$ . With Follow-up, we established that benign lung nodules show significant reduction, stable at follow-up or complete resolution.

**Aim of the Work:** The aim of this study is to evaluate FDG PET/CT prognostic performance in pulmonary nodules detected in oncological patients to correctly stage and treat primary cancer saving the patient valuable time.

**Conclusions:** FDG PET/CT is a valuable complementary tool to conventional imaging methods for the evaluation of benign and malignant pulmonary nodules to correctly stage and treat primary cancer saving the patient valuable time.

**Key Words:** Pulmonary nodules – PET/CT – Primary tumors.

### Introduction

A **LUNG** nodule is defined as an approximately rounded opacity more or less well-defined measuring up to 3cm in diameter. Pulmonary nodules are classified as solid, partially solid and non-solid (ground-glass) [1].

Lung nodule have a broad differential diagnosis including neoplastic process, infections, inflammation, congenital and vascular [2].

#### List of Abbreviations:

18F-FDG: 18-fluorine fluorodeoxyglucose.  
PET : Positron emission tomography-computed tomography.  
DICOM : Digital Imaging and Communications in Medicine.  
ROC : Receiver operating characteristic curve.  
ROI : Region of interest.  
SPSS : Statistical package for social science.  
SUVmax : Maximum standardized uptake value.

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Metastatic lung nodules are among the important differential diagnoses of pulmonary nodules as the lungs are the second most frequent site of metastases. Lungs are the second most frequent site of metastases from extra thoracic malignancies, through the bloodstream or lymphatic system and they most typically appear as well-circumscribed, noncalcified nodules. Pulmonary metastases indicate disseminated disease and place the patient in stage IV in TNM staging systems which alters the management plan [3].

Conventional radiological methods can provide detailed information about their morphology such as size, location, tissue characterization only. Modalities such as CT or MRI could not distinguish between benign and malignant tumors accurately [4].

F-18 FDG PET/CT plays an important role in the differential diagnosis of benign and malignant lung nodules detected during follow-up. PET images allow both a visual and quantitative evaluation. The glucose utilization of tissues can be semi-quantitatively defined by SUVmax. The detection of small pulmonary nodules is essential for appropriate staging and management of patients with malignancy [5].

FDG PET/CT play role as complementary to conventional imaging methods in the diagnostic work-up of indeterminate lung nodules identified on low dose CT in patients with known primary cancer screening. PET/CT may reduce unnecessary invasive intervention for diagnosis in patients with non-avid or low avid FDG lesions [1].

### Patients and Methods

Those patients were referred to the Radio Diagnosis & Nuclear Medicine Departments in El Kasr Aini Cairo University and private center for PET CT of the chest over a over a period of 6 month from July 2021 to January 2022.

This study included 80 patients with positive history of known primary tumor, underwent follow-up study (over period of 6 months) for the most active nodules which are 113 pulmonary nodules (20 solitary, 93 multiple).

#### *Inclusion criteria:*

- Pulmonary nodules detected on CT in current or previously treated malignancy.
- Patients diagnosed with pulmonary or extra pulmonary primary tumor receiving no treatment during the period of follow-up.

#### *Exclusion criteria:*

- Pregnant patient.
- Patient with uncontrolled diabetes mellitus
- Renal patients with elevated serum creatinine level.
- Known allergy to contrast media.

*All cases were subjected to the following:*

- Informed written consent was obtained from all patients prior to enrollment.
- Clinical evaluation by complete past and present history.
- Laboratory studies including: Blood glucose level, blood urea and creatinine.

#### *Protocol for PET/CT study:*

##### *PET imaging and analysis:*

Eighty patients were studied using 18-FDG. FDG was prepared using an automated synthesis system, and quality assurance tests were performed on Philips GE PET/CT equipment.

After a transmission scan using germanium-68/gallium-68 ring source for the attenuation correction, a bolus dose of FDG was injected intravenously. The mean dose of FDG was  $4.8 \pm 0.8$  mCi ( $177.6 \pm 29.6$  MBq) according patient's body weight.

Dynamic images were obtained first, followed by a 10min static image that was acquired 45min after injection of FDG.

The PET images were reconstructed using a measured attenuation, dead time and decay correction factors. There was no significant patient movement or mis-positioning between transmission scan and emission scan. This was checked with the markers attached to the patient and the laser pointers of the scanner during the examination.

In order to have the anatomical orientation of the PET image, CT images were used being fused with PET images using the attenuation corrected series.

Combined PET/CT images were transferred to workstation to be analyzed and evaluated by combined team of nuclear medicine and radiology specialties.

Negative results were considered if the lung nodule showed FDG uptake less than the mediastinal background activity. If the lung nodule showed uptake equal to or higher than the mediastinal uptake activity, it was considered as a positive result.

Then, the lung nodule uptake was assessed using the Region of Interest (ROI) technique. The lung nodule ROI was set on the static image. The nodules ROIs were checked carefully using the most active one independent on size by superimposing both on transmission images and on the early post injection images, which showed vascular structures. The mean radioactivity per pixel within the nodule ROI was quantitatively analyzed by calculating standardized uptake value (SUV).

The maximum standardized uptake value (SUVmax) of the lung nodules was measured either manually or automatic quantification technology

according to type of device and choose the most active nodule if multiple.

Malignant or benign classification of the nodules was determined by the radiological follow-up, clinical history and pathology in limited cases.

*Benign if they have one of any criteria over 6 months:*

- Initially low metabolic activity and remain low after follow-up.
- Relatively high SUVmax and decreased at follow-up as in infection.
- Resolved (non-avid FDG).

Malignant if they have Initial high SUVmax and remain high or show increasing metabolic activity or newly developed nodules with high SUVmax at follow-up.

*Statistical analysis:*

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test (Chan, 2003a). For comparing categorical data, Chi square ( $\chi^2$ ) test was performed. Exact test was used instead when the expected frequency is less than 5 (Chan, 2003b). ROC curve was constructed with area under curve analysis performed to detect best cutoff value of SUVmax for detection of malignancy. *p*-values less than 0.05 were considered as statistically significant.

## Results

This study involved 80 oncological patients (60 patients with multiple lung nodules and 20 patients with a solitary lung nodule). The mean age of the patients was 59 years with the youngest patient was 35-year-old and the oldest patient was 77-year-old. Among 80 patients, 30 patients were females (37.5%) while 50 patients were males (62.5%).

The primary cancers in these patients were: Lung (20 patients), colo-rectal (15 patients), breast (17 patients), urological tract (kidney, bladder, prostate, 13 patients), head and neck (5 patients), ovarian and uterine (5 patients), Hodgkin lymphoma (3 patients) and 2 patients had more than one previous cancer (one has cancer breast and cancer rectum, the other has breast and ovarian tumor).

*In patients-based analysis:*

The prevalence of malignancy of pulmonary nodules in oncological patients was 61/80 (76.2%) with PET/CT provided sensitivity 93.4%, specificity

94.7%. ROC analysis (SUVmax cut-off = 1.475) with significant *p*-value <0.001.

Malignant nodules (as showing in Figs. 1,2) at follow-up have mean SUVmax  $8.34 \pm 6.76$ , while benign nodules at follow-up have mean SUVmax  $0.58 \pm 0.99$  with significant *p*-value <0.001. With Follow-up, we established that benign lung nodules show significant reduction, stable at follow-up or complete resolution.

Twenty patients with solitary lung nodule pattern, 14 of them (70%) suggestive to have malignant nodules and other 6 patients (30%) have suggestive benign nodules.

Sixty patients with multiple lung nodules pattern; 47 of them (78.4%) suggestive to have malignant nodules and other 13 patients (21.6%) suggestive to have benign nodules.

*In nodule-based analysis:*

Follow-up to 20 solitary nodules in 20 patients, we found 14 malignant lung nodules with prevalence of malignancy was 70%, while during follow-up of 93 multiple nodules (the most active ones) in 60 oncological patients, we found 64 malignant lung nodules with prevalence of malignancy was 68.8%.

In follow-up of 113 nodules (20 solitary, 93 multiple), we found 35 benign nodules, while 78 nodules were malignant nodules (prevalence of malignancy was 69%).

Regarding the diameter size of the pulmonary nodules, malignant nodules have mean size  $16.51 \pm 7.52$ mm, while benign nodules have mean size  $7.64 \pm 3.32$ mm with significant *p*-value <0.001.

*Regarding the size of the nodules through the follow-up, the following can be noted:*

- Benign nodules usually decreased in size with follow-up.
- Malignant nodules if increased in size with follow-up.

*Qualitative analysis:*

It is essential to understand the causes of both false positive and false negative results when interpreting PET/CT to avoid making inaccurate diagnoses.

Although PET-CT results according to their SUVmax values have shown that 61 cases considered as true positive with high SUVmax values, 4 cases were considered as false positive with high SUVmax value (>1.47). Two of them known to have sarcoidosis with clinical history and the same nodule distribution at the previously available CT films.

The other two show signs of infection as fever, wheezes and elevated CRP and ESR with good

response to anti-inflammatory drugs (regressive course regarding the size and the SUV max during the follow-up) (Fig. 3).

In limited cases with referral to pathology, we found 3 cases with false negative lung nodules, two of them with primary mucinous carcinoma of the breast and one case with primary renal cell carcinoma.

In the case of the renal cell carcinoma, a newly developed single lung nodule with SUVmax 1.3 and stable appearance during 6 months interval follow-up. We considered it as a benign nodule, but the clinician decided to take a biopsy due its doubt about type of low cellularity of the primary renal cell carcinoma. After the referral to the pathology, the result confirmed its metastatic nature.

The other two false negative nodules were secondaries to low cellular type of breast cancer. The

low cellularity of these tumors caused by the presence of mucin and slowly growing tumors results in lower FDG uptake of the nodules (with SUVmax also not increase during the follow-up).

We considered the as a benign nodule, but the clinician has a different opinion as he decided biopsy due to his doubt about the type of the primary tumor and to avoid delay in appropriate treatment.

After referral to the pathology, the opinion of the clinician was true opinion about relation between the type of the primary tumor and the pulmonary nodules.

Those types of tumors are one of our PET CT limitations.

*Provisional diagnosis:* Benign looking pulmonary nodules (infection).



Fig. (1): 68-years old male patient known pancreatic head cancer, underwent Whipple operation two years ago, referred for follow-up PET/CT examination. (A&C) Axial CT with fused PET of the previous study, while (B&D) are axial CT with fused PET for the current study. These images showed progression in size, number and metabolic activity of the bilateral pulmonary nodules with the largest and most active one currently seen at the right lower lobe (posterior basal segment) measuring 16 x 12 mm in diameter and achieving up to 8.35 SUVmax compared to non-avid nodules in the previous study.

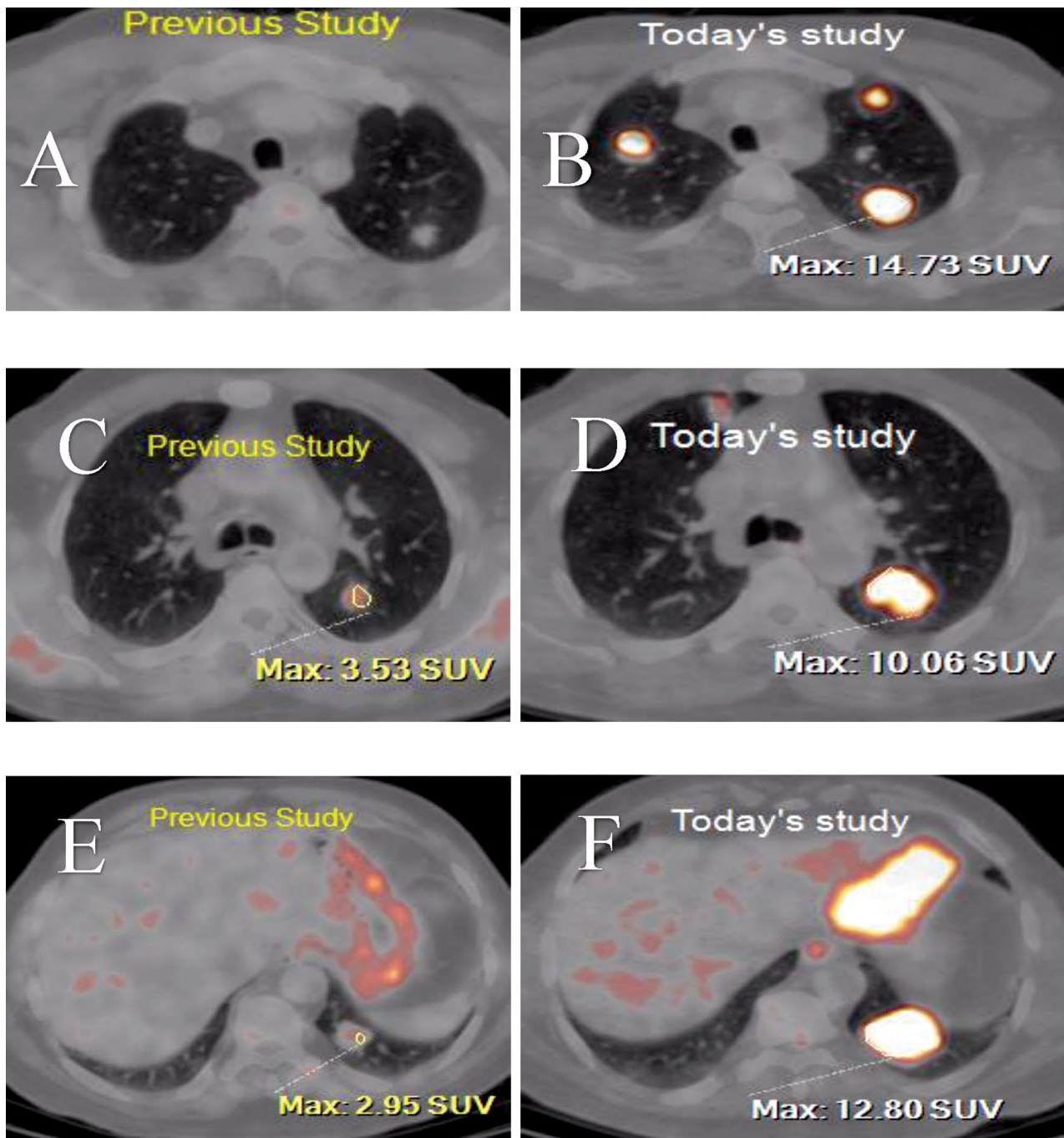


Fig. (2): 49-year-old male patient, presented with history of metastatic urinary bladder cancer, underwent cystoscopic excision followed by local BCG injection referred for follow-up PET/CT examination. (A, C & E) Axial CT with fused PET of the previous study, while (B, D & F) are axial CT with fused PET for the current study. These images showed significant progression in size, number and metabolic activity of the previously detected multiple bilateral pulmonary nodules, the largest was currently seen at the left upper lobe apico-posterior segment, achieving up to 14.73 SUVmax and measuring 23 x 21 mm in diameter (compared to 13 mm & 3.5 SUVmax previously noted nodule at the apico-posterior segment of the left upper lung lobe).

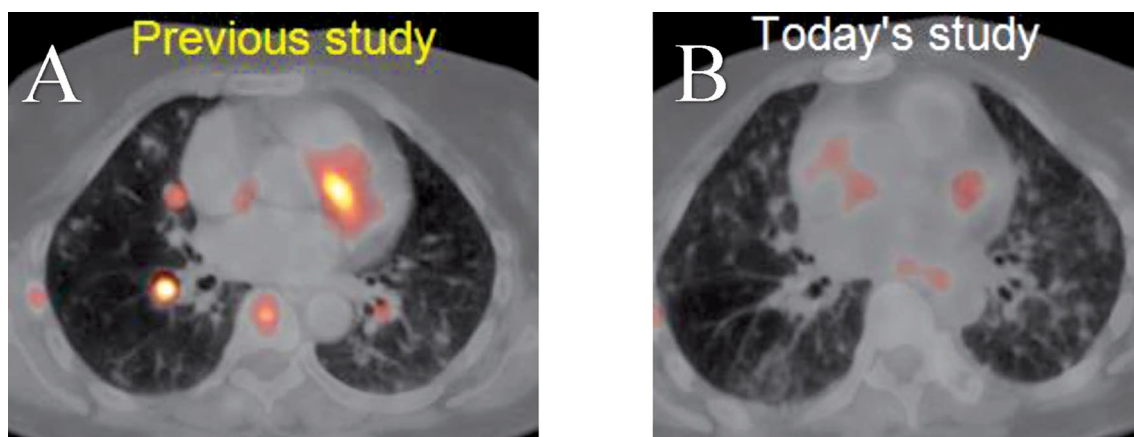


Fig. (3): 61-year-old female patient, with history of breast cancer complaining of recurrent fever, cough and dyspnea and receiving anti-inflammatory drugs referred for PET CT. (A) & (B) axial CT cuts with fused PET images for previous and current studies respectively. Axial CT with fused PET during 6 months follow-up showed complete metabolic resolution of the bilateral pulmonary nodules with no abnormal activity recently detected compared to previous study with low SUVmax (1.2) after receiving anti-inflammatory drugs.

### Discussion

Detection of malignant pulmonary nodules in patients with history of malignant neoplasm is crucial and carries great impact on the therapeutic strategy and the plan of management [6].

CT has been the cornerstone of oncologic imaging but lacks the ability to show crucial differences in physiology. PET has incomparable abilities to determine the metabolic activity of tissues but needs the assistance of higher-resolution, anatomic information that it cannot provide. CT is the easiest and highest-resolution tomographic modality to integrate into PET imaging. The combination of the two offers the best of both worlds in an integrated data set and thus improves diagnostic accuracy and localization of many lesions [7].

Our study included 80 patients 50 males (62.5%) & 30 females (37.5%).

In our study, the prevalence of malignancy was 76.2% with sensitivity 93.4%, specificity 94.7% and ROC analysis showing SUVmax cut-off=1.475 with significant  $p$ -value <0.001.

These results were in agreement with that reported in oncological populations as in studies performed by Khokhar et al. [8] and Taralli et al. [6]. In the study carried out by Taralli et al. [6], the prevalence of malignancy was 75.8%, with ROC analysis using 1.7 SUVmax as cut-off value providing specificity 72.7% and sensitivity 85.5% with significant  $p$ -value <0.001.

In a study done by Yee Ting Sim et al. [9], they correlated SUVmax value with pathology of single pulmonary nodule (SPN) and assessed diagnostic accuracy in differentiating malignant from benign nodule, using 2.5 as threshold SUVmax demon-

strating that accuracy of PET/CT in diagnosing malignant SPN was 81.2% with sensitivity 86.7%, specificity 50% which was near to pathology confirmation.

In Khalaf et al. [10], they evaluate the relation between SUVmax and size of nodule as no pre-determined fixed SUVmax cut off value as 2.5 is able to differentiate pulmonary nodules as definitely benign or definitely malignant regardless of the nodule size. The sensitivity and the accuracy of the test using SUVmax cutoff of 2.5 are increased with an increase in the diameter of pulmonary nodules. Although, The SUVmax cutoff of 2.5 is a useful tool in the evaluation of large pulmonary nodules (>1.0 cm), it has no or minimal value in the evaluation of small pulmonary nodules (<or=1.0cm).

In this study, many small pulmonary nodules <1cm presented with SUVmax more than 2.5 and resulted in false positive PET scan as in (granuloma, infection and rheumatoid nodule). On the other hand, well differentiated and slow growing malignant nodules presented with SUVmax less than 2.5. So, this study recommended to lower SUVmax in small pulmonary nodule (< or =1cm).

In a study carried out by Taralli et al. [6], the prevalence of malignancy in solitary and multiple nodules was 87.6% and 52.5% respectively. This result was close to our study result that showed that the prevalence of malignancy in solitary nodules was 70%, while in multiple nodules the prevalence of malignancy was 68.8%.

So, relation between solitary/multiple nodules pattern and prevalence of malignancy revealed no statistically significant relation between them.

Our study and Taralli et al. [6] study demonstrate that multiplicity not one of sure sign of malignancy

as we found that the rate of malignancy is higher in solitary ones.

In our study, there was multiple nodules turned to be benign (likely due to inflammatory processes) as they disappeared or reduced through the follow-up study.

Regarding nodule size, malignant nodules had significantly larger size and higher metabolic activity than benign ones with significant difference was observed in size ( $p < 0.0001$ ) in Taralli et al. [6] with mean size of the malignant nodules about  $16.5 \pm 8.1$  mm.

This comes in agreement with our study that demonstrated mean size of the malignant nodules about  $16.51 \pm 7.52$  mm, while benign nodules have mean size about  $7.64 \pm 3.32$  mm with  $p$ -value  $< 0.001$ .

In comparison of malignant and benign nodules, the malignant nodules usually show larger size and higher FDG activity regardless being solitary or multiple nodules.

In study of Reinhardt et al. [12] said that pulmonary metastases of 8–10 mm in diameter can be accurately detected by PET-CT with a sensitivity of 78%. The sensitivity of PET increased to 94% and more for pulmonary metastases measuring at least 11 mm in size, but dropped to 40% for nodules 5–7 mm in diameter. No metastases smaller than 5 mm in diameter were seen on PET images.

In De Wever et al. [13] study, cannot differentiate nodules smaller than 5 mm with integrated PET-CT, but nodules larger than 5 mm could be differentiated with integrated PET-CT. They said that an accurate evaluation is only possible in lesions larger than 1 cm as they could not demonstrate a significant difference between PET-CT and CT in the detection of small pulmonary metastases as detection of nodules with integrated PET-CT is based on the detection of these nodules with CT.

Overall, the FDG PET/CT is a powerful new diagnostic tool that has made a significant contribution to the diagnosis and management of oncology patients. We should be aware about false positive and false negative when interpreting PET/CT to avoid making inaccurate diagnoses.

FDG is not only a cancer specific imaging agent as false positive results may be observed with benign diseases [14].

False positive results are commonly observed with active inflammation or infection as in our study where 2 cases of infection (presented with fever and high laboratory labs) have been detected and showed reduction of SUVmax reading at the follow-up study as a response to anti-inflammatory therapy. The explanation for this pitfall that inflammatory cells have markedly increased glycolysis.

The other 2 cases were presented with sarcoidosis and they were diagnosed with clinical history. During the comparison with the last CT studies, the current PET/CT showed no changes in the site and metabolic activity of the previously detected nodules as well as the bilateral hilar and mediastinal nodal distribution. The explanation of high SUVmax (8.1) was that inflammatory cells such as accumulated T-lymphocytes, mononuclear phagocytes, non-caseating epithelioid granulomas cause tracer accumulation at the affected sites.

In our study, three false negative cases detected depending on pathology as two cases of mucinous carcinoma of the breast and one case of renal cell carcinoma, which is considered as one of our limitations as benign nodules but after referral to pathology which determine their malignant nature.

Study carried out by Chang et al. [15] have stated that tumors with low-cellularity show low-glucose metabolizing pattern as detected in mucinous tumors and they are well-known major causes of false negative findings.

### Conclusions:

In conclusion, FDG PET/CT is a valuable imaging tool in the evaluation of benign and malignant pulmonary nodules to correctly stage and treat primary cancer saving the patient valuable time.

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## دور التصوير المقطعي المحوسب بالانبعاث البوزيتروني في الكشف عن العقيدات الرئوية لدى المرضى الذين يعانون من الورم الرئوي المعروف

نسبه حدوث العقيدات الرئوية الخبيثة في مرضى الاورام اعلى من المرضى الذين لا يعانون من الاورام في حين ان طبيعتهم الحميدة لا يمكن استبعادها بالكامل.

وجود الثانويات الرئوية يعنى انتشار المرض و وضع المريض في المرحلة الرابعة من السرطان مما يغير في خطه العلاج.

يمكن تمييز العقيدات الرئوية الحميدة والخبيثة اعتمادا PET CT حيث يتمتع PET بقدرات لا تضاهى لتحديد النشاط الأيضي للأنسجة ولكنها تحتاج إلى مساعدة معلومات تشريحية عالية الدقة لا تستطيع توفيرها.

الهدف من الدراسة التمييز بين العقيدات الرئوية الحميدة والخبيثة باستخدام قيم Suvmax والحجم وذلك بمتابعه الأشعة خلال ٦ شهور والتقييم الإكلينيكي.

يمثل Suvmax أعلى نقطة في النشاط الأيضي، وبالتالي يعكس المنطقة الأكثر عدوانية من الناحية البيولوجية حيث وجدنا ان العقيدات الرئوية الخبيثة لها قيمه اعلى من SUVmax وحجم اكبر من الحميدة.

من النظرة الإكلينيكية وجود عده عقيدات رئوية في مرضى الاورام يمثل ذلك انها خبيثة وهذا انتشار للورم الاولى.

دراستنا وجدت ان لا علاقة بين عدد العقيدات الرئوية وطبيعتها الحميدة او الخبيثة، بل وجدونا ان نسبه عدوانيه العقيدات الرئوية الانفرادية اعلى من المتعددة وايضا لا علاقة بين مكان العقد الرئوية او شكلها ومدى عدوانيتها.