

Application of ¹⁸F-FDG PET-CT in the management of pulmonary nodule and mass – a pictorial review

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SUMMARY

Background: Lung cancer is one of the leading causes of cancer-related mortality worldwide. Pulmonary nodules are commonly encountered in clinical practice because of the recent implementation of low-dose CT lung screening programme, incidental finding on cardiac CT or CT for non-thoracic related disease. ¹⁸F-FDG PET-CT plays an important role in the management of pulmonary nodules.

Methods: In this pictorial review, we present six different scenarios of using ¹⁸F-FDG PET-CT in the management of suspicious pulmonary nodule or mass. The advantages and limitations of ¹⁸F-FDG PET-CT and Herder model are discussed.

Results: ¹⁸F-FDG PET-CT with risk assessment using Herder model provides added value in characterising indeterminate pulmonary nodules. Besides, ¹⁸F-FDG PET-CT is valuable to guide the site of biopsy and provide accurate staging of lung cancer.

Conclusion: To further improve its diagnostic accuracy, careful history taking, and CT morphological evaluation should be taken into consideration when interpreting ¹⁸F-FDG PET-CT findings in patients with these nodules.

KEY WORDS:

Pulmonary nodule; ¹⁸F-FDG; PET-CT; lung cancer; Herder model

INTRODUCTION

Lung cancer is one of the leading causes of cancer-related mortality worldwide. The incidence of lung cancer has been increasing in many developing countries while decreasing in several high-income countries.¹ In 2014 alone, over 4400 cases of lung cancers were diagnosed in Malaysia with a 75% male preponderance.² It accounts for 24.6% and 13.0% of all cancer mortality in male and female Malaysians, respectively.²

As high as 53.9% of lung cancers patients, who are asymptomatic at diagnosis, are more likely to be diagnosed at earlier stages and thus have better survival rates.^{3,4} Due to the higher detection rate of lung cancers by computed tomography (CT) scan compared with chest radiograph, the US Preventive Services Task Force (USPSTF) has recommended

annual low-dose CT screening in 'high risk' adults aged 55 to 80 years who have history of smoking of >30 pack-years within the past 15 years.^{5,6} However, as majority of these incidentally detected pulmonary nodules are benign, such a wide-scale screening approach may result in unnecessary invasive intervention or time-consuming follow-up.⁷ In the NELSON trial, the probabilities of lung cancers detected by low-dose CT screening were low, in particular with small nodules.⁸ Subsequently, the American College of Radiology (ACR) has proposed recommendations to solve these issues despite with some limitations.⁹

In addition, the Fleischner Society guideline has suggested a management approach for incidentally encountered pulmonary nodules on CT in adult patients aged over 35 years old unrelated to a lung cancer screening programme.¹⁰ The presence of many guidelines reflects the complexity of this issue and creates confusion among physicians. Not to mention that these existing guidelines are not applicable for the patients with known primary cancers at risk of lung metastases or those suspected of having infective pulmonary nodules.

As many of the lung cancers demonstrate glucose hypermetabolism, imaging utilising a radiolabelled glucose analogue, positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (¹⁸F-FDG PET-CT), plays an important role in the management of the pulmonary nodules.¹¹ The British Thoracic Society (BTS) guideline recommends ¹⁸F-FDG PET-CT imaging if the Brock model, a composite scoring based on a number of clinical risk factors and CT findings, demonstrates >10% risk of malignancy.¹² It also recommends the Herder model to derive the percentage of malignancy risk from the ¹⁸F-FDG PET-CT findings.¹² Subsequent management plan is based on the estimated risk score from Herder model. In contrast to the management based on interval CT monitoring, such approach can reduce time to diagnosis.

By illustrating the following cases, we explain the roles and limitations of ¹⁸F-FDG PET-CT in managing the pulmonary nodules and lung mass with particular attention to the Herder model. It is hoped that heterogeneity of the clinical practices can be reduced by providing a clear guidance on definitive management of the pulmonary nodules.

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Case 1 Indeterminate pulmonary nodule

A 79-year-old woman who was an ex-smoker presented with an incidental finding of a solid nodule at the right lower lobe on cardiac CT during a medical check-up. Subsequent CT demonstrated progression in the nodule size, measuring 28 x 19mm. The Brock model estimated a cancer probability of 64.94%. As she declined invasive CT guided biopsy, she was further evaluated with ¹⁸F-FDG PET-CT.

¹⁸F-FDG PET-CT demonstrated high ¹⁸F-FDG uptake in the right lung nodule (maximum standardised uptake value [SUV_{max}] 5.1) (Figure 1). Using the Herder model, the cancer risk was re-calculated to be 95.8%. Right lower lobectomy was performed, and the resected specimen revealed moderately differentiated invasive adenocarcinoma.

This case demonstrates the usefulness of Herder model to inform the necessity and urgency of histopathologic confirmation in order to shorten the duration of follow-up. On PET-CT images, the nodules are classified on four-point score according to ¹⁸F-FDG uptake i.e., absent, faint, moderate and intense, using mediastinal blood pool activity as the reference. The Herder model incorporates the Swensen model (risk factor scoring comprising age, smoking status, history of extra-thoracic cancer, nodule size, location and spiculation) and ¹⁸F-FDG uptake score to obtain the percentage of cancer probability. The equations for the calculation of Herder and Swensen models are shown below.

Herder model:

Probability of malignancy = $1/(1 + e^{-x})$, where $x = -4.739 + 3.691$ (% of probability by the Swensen model) + 2.322 (faint uptake) + 4.617 (moderate uptake) + 4.771 (intense uptake).

Swensen model:

Probability of malignancy = $1/(1 + e^{-x})$, where $x = -6.8272 + 0.0391$ (age) + 0.7917 (cigarettes) + 1.3388 (cancer) + 0.1274 (diameter) + 1.0407 (spiculation) + 0.7838 (upper) [Age is the patient's age (in years); cigarettes is 1 if the patient is a current or former smoker (otherwise, 0); cancer is 1 if the patient has a history of extrathoracic cancer that had been diagnosed >5 years ago (otherwise, 0); diameter is the diameter of the solitary pulmonary nodule, SPN (in millimetres), spiculation is 1 if the edge of the SPN has spicula (otherwise, 0); and upper is 1 if the SPN is located in an upper lobe (otherwise, 0).]

This method yields an area under the receiver operating characteristic curve of 0.92, indicating high overall accuracy.¹³ A convenient calculator of Herder model is available online.

Case 2 Bronchioloalveolar carcinoma with low ¹⁸F-FDG activity

A 40-year-old man who was a chronic smoker presented with cough. CT thorax showed a solid nodule in the right middle lobe. Six months later, a surveillance CT showed an increase in nodular size (measuring 19 x 21mm). The Brock model predicted a 16.8% risk of malignancy. Hence, ¹⁸F-FDG PET-CT was performed for further risk stratification. It demonstrated moderate ¹⁸F-FDG uptake higher than mediastinal blood pool (SUV_{max} 2.0) (Figure 2), resulting in an estimated malignancy risk of 22.5% on the basis of Herder model.

As the patient was in the intermediate risk category based on the Herder model, he was offered the options of CT-guided biopsy, excision biopsy or CT surveillance.¹² CT-guided needle biopsy was eventually performed, and the specimen results confirmed invasive adenocarcinoma of the bronchioloalveolar subtype.

The key message of this case is that lung malignancy cannot be excluded solely by the absence of high ¹⁸F-FDG uptake (conventionally, lesions with SUV_{max}<2.5 are considered benign). Tumour size and growth rate remain important indicators of the nature of pulmonary nodules.¹⁴ In this case, interval tumour size progression and intermediate malignancy risk based on the Herder model warranted histopathological confirmation.

Bronchioloalveolar carcinoma is an indolent subtype of lung adenocarcinoma. It carries better prognosis compared with the acinar, papillary and solid subtypes.¹⁵ A study by Vasselle et al., demonstrates significant differences in ¹⁸F-FDG uptake across various histologic subtypes and cellular differentiation of non-small cell lung carcinoma. ¹⁸F-FDG uptake is the lowest in bronchioloalveolar adenocarcinoma and the highest in squamous cell and large cell phenotypes. In the same study, ¹⁸F-FDG uptake correlates well with the Ki-67 proliferative index.¹⁶

In addition to its ability to predict the histologic subtypes, ¹⁸F-FDG PET-CT also has prognostic value in non-small cell lung carcinoma. Meta-analysis has shown that SUV_{max}, metabolic tumour volume and total lesion glycolysis are predictive of both disease-free survival and overall survival.¹⁷ In another study, a SUV_{max} cut-off value of 6.7 significantly affected prognosis, where the 2-year disease-specific survival was 91% for SUV_{max}≤6.7 versus 55% for SUV_{max}>6.7.¹⁸

Case 3 Pre-operative tumour staging

A 67-year-old man who was an ex-smoker presented with haemoptysis. CT thorax showed a large mass in the right middle lobe with a small indeterminate nodule in the left lower lobe. ¹⁸F-FDG PET-CT was performed to determine the nature of the contralateral nodule. Subsequent respiratory gated PET-CT showed intense ¹⁸F-FDG uptake in the right lung mass as well as the contralateral lung nodule (arrow in Figure 3). In addition, ¹⁸F-FDG avid enlarged subcarinal node and lytic lesion at left second rib (arrow head in Figure 3) were demonstrated, indicating M1 disease. CT-guided biopsy of the right middle lobe mass showed squamous cell carcinoma. This case highlighted not only the importance of ¹⁸F-FDG PET-CT for pre-operative staging of clinically diagnosed lung cancer but also the limitation of Herder model whereby it cannot be used to evaluate PN in patients with existing lung cancer.

¹⁸F-FDG PET-CT is recommended to stage all newly diagnosed non-small cell lung carcinoma due to its ability to detect mediastinal nodal and distant metastases. A meta-analysis by Wu et al., incorporating 56 studies of over 8700 patients demonstrated intermediate sensitivity and high specificity of ¹⁸F-FDG PET-CT in N and M staging with pooled sensitivity and specificity of (0.72 and 0.91) and (0.77 and 0.95), respectively.¹⁹ Furthermore, in evaluating bone metastases,

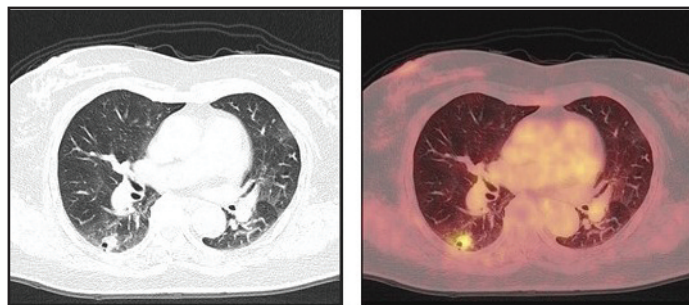


Fig. 1: ¹⁸F-FDG PET-CT showed hypermetabolic spiculated nodule in superior segment of right lower lobe, which was confirmed to be adenocarcinoma.

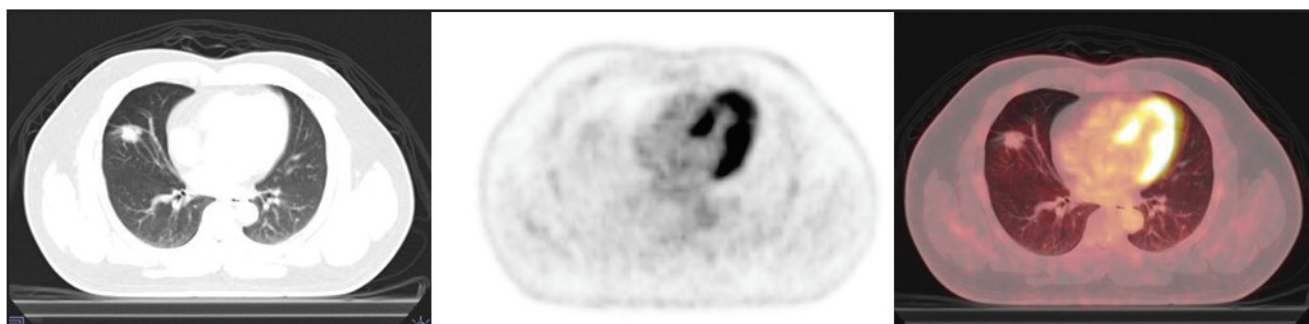


Fig. 2: ¹⁸F-FDG PET-CT showed right middle lobe pulmonary nodule with mild ¹⁸F-FDG uptake, it was histopathologically confirmed to be bronchoalveolar carcinoma.

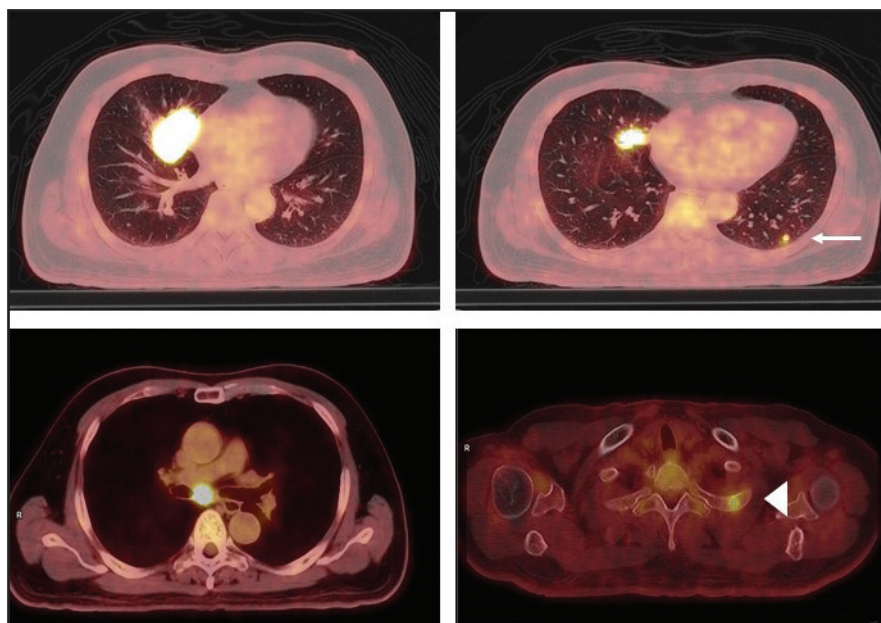


Fig. 3: ¹⁸F-FDG PET-CT showed intensely hypermetabolic squamous cell carcinoma of right middle lobe with metastases to mediastinal lymph node and contralateral lung (arrow), as well as unsuspected bone metastasis (arrow head).

the pooled sensitivity and specificity were 0.91 and 0.98, respectively.¹⁹

Despite limited view on certain nodal stations, endoscopic or endobronchial ultrasound or mediastinoscopy has higher sensitivity in detecting nodal metastasis compared with CT and ¹⁸F-FDG PET-CT.²⁰ Hence, endoscopic or endobronchial

ultrasound or mediastinoscopy is still considered mandatory for mediastinal nodal evaluation. In the case of peripheral T1 tumour, where the likelihood of nodal metastasis is low, such invasive approach may be optional.²⁰ Nevertheless, ¹⁸F-FDG PET-CT is a non-invasive screening tool in evaluating nodal and distant metastasis, which can dramatically alter the subsequent management plan.

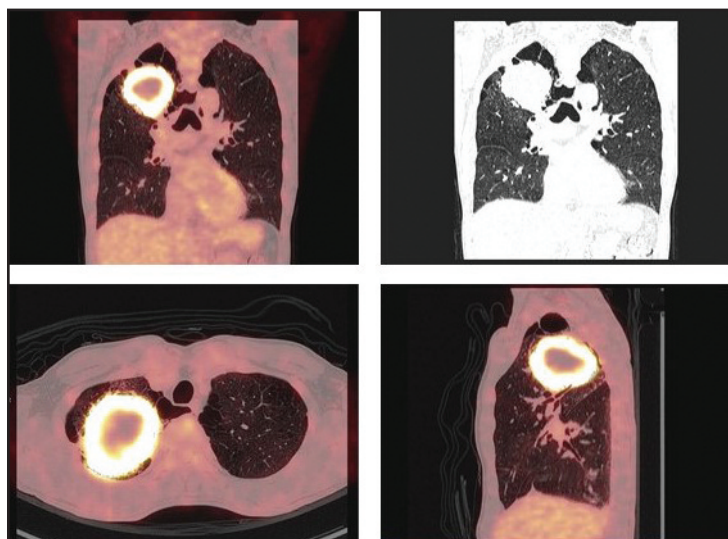


Fig. 4: ^{18}F -FDG PET-CT showed large right upper lobe lung mass with intense ^{18}F -FDG uptake at the periphery of the mass and necrotic centre devoid of ^{18}F -FDG activity. After two unsuccessful random biopsies, PET-CT guided biopsy targeting hypermetabolic region of the mass confirmed poorly differentiated adenocarcinoma.

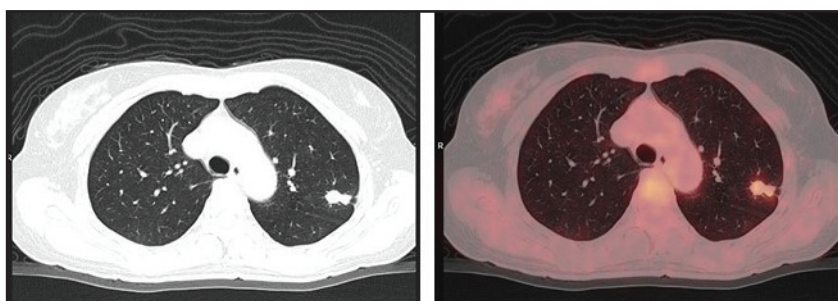


Fig. 5: ^{18}F -FDG PET-CT demonstrated two coalescing spiculated nodules at the periphery of apicoposterior segment of left upper lobe with moderate ^{18}F -FDG avidity, confirmed to be false positive lesions due to tuberculosis.

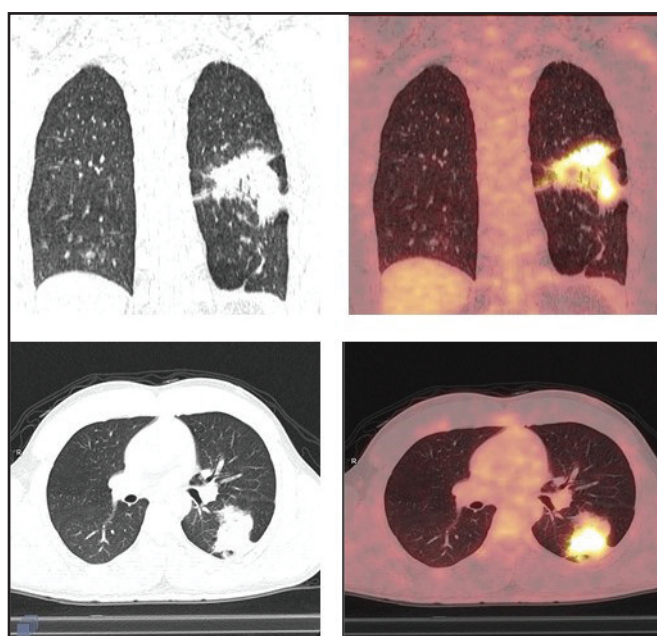


Fig. 6: ^{18}F -FDG PET-CT of Case 6 with atypical presentation of pneumonia, demonstrated heterogenous ^{18}F -FDG uptake in superior segment of left lower lobe, corresponding to consolidative changes on CT. This finding was in contrast to that of bronchogenic carcinoma, usually showing centrally located intense hypermetabolic lesion associated with less intense ^{18}F -FDG uptake in peripheral collapse/ consolidation. Mucinous adenocarcinoma also has consolidative appearance on CT but usually with minimal ^{18}F -FDG uptake. Biopsy confirmed pneumonia in this case.

Case 4 Guiding biopsy

A 49-year-old man who presented with haemoptysis was referred for further evaluation of a large right lung mass measuring 80mm in the longest dimension. Two consecutive CT-guided needle biopsies revealed only inflammation. Despite high suspicion of malignancy, the patient was reluctant to undergo third CT-guided needle biopsy. ¹⁸F-FDG PET-CT demonstrated intense ¹⁸F-FDG uptake at the periphery of the mass (SUVmax 17.0) with a large area of central ametabolism, suggesting central necrosis (Figure 4). Subsequently, a third CT-guided biopsy directed at the hypermetabolic area of the mass shown by ¹⁸F-FDG PET-CT confirmed the diagnosis of poorly differentiated adenocarcinoma.

Central necrosis is a common feature of primary lung malignancies, in particular squamous cell and large cell carcinomas.²¹ Central necrosis is thought to be a consequence of rapid tumoural growth which exceeds the capacity of neoangiogenesis resulting in ischaemic tumour necrosis.²¹ As metabolism is only visualised in viable cells, ¹⁸F-FDG PET-CT is a valuable tool to differentiate viable from necrotic areas in a large tumour. This enhances the diagnostic yield of PET-CT-guided biopsy.

Case 5 Tuberculoma as a pitfall in 18F-FDG PET-CT

A 44-year-old woman was incidentally found to have two small coalescing lung nodules with spiculated margin measuring a total of 19mm in the longest dimension in the left upper lobe during cardiac CT evaluation. Anamnesis did not elicit recent or remote history of chest infections. She was never a smoker. Malignancy risk estimation based on the Brock model was 37.7%. ¹⁸F-FDG PET-CT revealed moderate intensity of ¹⁸F-FDG uptake (SUVmax 2.53) (Figure 5). The estimated malignancy risk based on the Herder model was 73.0%. Subsequent CT-guided biopsy revealed the presence of caseating granulomata with acid-fast bacilli on Zielh-Neelson staining, consistent with tuberculosis.

Glucose hypermetabolism is unfortunately not exclusively confined to cancer cells, thus limiting the specificity of ¹⁸F-FDG PET-CT. In evaluating pulmonary nodules, high ¹⁸F-FDG uptake can be due to infective or inflammatory pathologies in which there is high glucose metabolism by activated neutrophils and macrophages.²²

With the advent of hybrid PET-CT, the pattern on PET-CT may help to distinguish between infective lesion from malignancy. However, in some patients, asymptomatic tuberculoma may present as a nodule with intense ¹⁸F-FDG avidity and also CT features mimicking lung cancer such as spiculation, contrast enhancement and satellite lesions.²³ Histological confirmations usually cannot be spared in these scenarios.

Case 6 Pneumonia as a pitfall in 18F-FDG PET-CT

A 31-year-old man who had never smoked presented with an incidental finding of mildly elevated serum CA-19-9 but normal carcinoembryonic antigen marker during medical examination. He claimed to have a slight cough but denied fever or chest pain. CT scans of the thorax and abdomen

revealed consolidation in the superior segment of the left lower lobe. ¹⁸F-FDG PET-CT performed for further evaluation revealed intense heterogenous ¹⁸F-FDG uptake (SUVmax 11.2) in the consolidation (Figure 6). Despite high ¹⁸F-FDG uptake, the heterogeneity of uptake on PET and appearance of segmental consolidation on CT suggests the likelihood of an infective lesion. Subsequent CT-guided needle biopsy confirmed inflammatory in nature. The patient was treated with antibiotics and made an uneventful recovery.

Again, the clinical history and CT morphological evaluation cannot be overemphasised when interpreting pulmonary nodules on PET-CT. However, distinguishing segmental consolidation or round pneumonia from malignancy can sometimes be challenging.

Dual time point PET-CT imaging has yielded some success in distinguishing benign from malignant nodules.²⁴⁻²⁶ It was postulated that cancer cells and inflammatory cells manifest high glucose metabolism but only cancer cells show continuous accumulation of ¹⁸F-FDG whereas inflammatory cells show either static or washout of ¹⁸F-FDG on delayed imaging.²⁶ The washout of ¹⁸F-FDG is partly related to a higher expression of dephosphorylase enzyme in inflammatory cells compared to cancer cells.²⁶ A recent meta-analysis involving 778 patients revealed a statistically non-significant trend toward higher sensitivity and moderate level of specificity of dual time point PET-CT imaging when compared with single time point imaging in diagnosing malignancy.²⁷ However, dual time point PET-CT imaging lacks specificity when being employed in tuberculosis endemic countries.²⁸

CONCLUSION

¹⁸F-FDG PET-CT with risk assessment using the validated Herder model²⁹⁻³⁰ provides added value in characterising indeterminate pulmonary nodules, leading to a shorter time to diagnosis, better treatment outcome and cost saving. In the management of lung cancer, ¹⁸F-FDG PET-CT is essential to improve the accuracy of biopsy and staging. Despite its high accuracy, false positive and false negative do occur. To overcome such limitations and improve its diagnostic accuracy, careful history taking, and CT morphological evaluation should be taken into consideration when interpreting ¹⁸F-FDG PET-CT findings in patients with lung nodules.

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Questions:

- 1. Regarding the solitary pulmonary nodule:**
 - A. Screening for lung cancer is recommended for the high risk population over the age of 50 years old.
 - B. Majority of the incidentally detected indeterminate solitary pulmonary nodules are benign.
 - C. Spiculated margin is a feature of a malignant lung nodule.
 - D. Volumetry is more sensitive than two-dimensional measurement in detecting the change of the nodular size on CT.
 - E. Tuberculosis is an unlikely cause of an asymptomatic lung nodule.

- 2. Regarding Herder model:**
 - A. It is used to estimate the risk of malignancy for a solitary pulmonary nodule.
 - B. It combines Brock model with the findings of the ¹⁸F-FDG PET-CT.
 - C. ¹⁸F-FDG PET-CT is recommended if the risk of lung malignancy as estimated by Brock model exceeds 20 percent.
 - D. Patients with intermediate risk of lung malignancy based on Herder model can be offered the options of CT-guided biopsy, excision biopsy or CT surveillance.
 - E. Herder model can be used to evaluate the possibility of a metastatic lung nodule.

- 3. The usefulness of 18F-FDG PET-CT include:**
 - A. Risk stratification of the solitary pulmonary nodule.
 - B. Staging of newly diagnosed squamous cell carcinoma of the lung.
 - C. To replace the mediastinal lymph node biopsy for N staging.
 - D. To guide the biopsy of a suspicious lung mass.
 - E. For prognostication of the lung cancer.

- 4. Regarding the findings of 18F-FDG PET-CT in non-small cell lung cancer:**
 - A. Large cell carcinoma shows low ¹⁸F-FDG uptake.
 - B. Mucinous adenocarcinoma and bronchoalveolar carcinoma are common causes of a false negative finding.
 - C. ¹⁸F-FDG uptake of the lung malignancy correlates with Ki-67 index.
 - D. Of all the ¹⁸F-FDG PET-CT parameters, only the metabolic tumour volume is predictive of the overall survival.
 - E. The brain metastases are difficult to be excluded by ¹⁸F-FDG PET-CT.

- 5. Pitfalls of ¹⁸F-FDG PET-CT:**
 - A. Activated neutrophils and macrophages demonstrate glucose hypermetabolism.
 - B. The pattern of ¹⁸F-FDG uptake helps to distinguish the causes of segmental lung consolidation.
 - C. Dual time point imaging has moderate specificity to distinguish the malignant lung nodule from the tuberculoma.
 - D. SUVmax cut-off of more than 10 is diagnostic of the lung cancer.
 - E. Parasitic granuloma can mimic the lung malignancy on the ¹⁸F-FDG PET-CT imaging.