



## FDG-PET/CT in the Evaluation of Pulmonary Nodules

- **Pulmonary nodules  $\leq 4$  mm have a low risk of being malignant; nodules between 4-8 mm are of intermediate risk for malignancy; follow up CT scans for both categories are recommended on different schedules**
- **Pulmonary nodules  $> 8$  mm and mixed solid/ground glass nodules are suspicious for malignancy; FDG - positron emission tomography (FDG-PET), percutaneous needle aspiration biopsy (PNAB), or video assisted thoracic surgery (VATS) should be considered**
- **A suggested guideline algorithm for the management of pulmonary nodules found on chest x-ray or CT is presented**

The finding of a solitary pulmonary nodule (SPN) on a chest radiograph is a common problem in pulmonary medicine. SPNs are caused by a variety of conditions, ranging from benign granulomas to lung cancer. Because solitary nodules are often malignant and because the 5 year survival after resection of a solitary bronchogenic carcinoma is as high as 80%, it is important to promptly identify malignant nodules to ensure optimal treatment. Similarly, it is important to avoid the morbidity and mortality associated with thoracotomy in patients with benign disease. Therefore, the goal of the evaluation and management of solitary pulmonary nodules is to promptly identify and bring to surgery all patients with operable malignant nodules while avoiding thoracotomy in patients with benign nodules.

The increased use of chest CT imaging has resulted in a dramatic escalation in the number of newly detected solitary pulmonary nodules, defined as round lesions  $< 3$  cm in diameter.

Size is an important predictor of the likelihood of malignancy and recent evidence indicates that pulmonary nodules  $\leq 4$  mm have an extremely small risk of cancer, especially in those with no history of cancer. In light of this new evidence, fewer short-term follow-up CT scans are necessary for most patients with small pulmonary nodules. Therefore, new recommendations have been developed for patient follow-up that varies according to the risk of cancer.

### Nodules with Low to Intermediate Risk

The likelihood of malignancy is  $< 1\%$  for nodules  $\leq 4$  mm and 6% for those between 4-8 mm. Nodules  $< 8$  mm are generally too small to biopsy percutaneously or to evaluate with a FDG-PET scan. Therefore, the best option is to watch and wait, with follow up CT scans at intervals that depend on nodule size, patient age, history of malignancy, and likelihood of infection (Figure 2).

Patients aged 18-35 yrs have a much smaller likelihood of malignancy than older adults ( $< 1\%$  of all lung cancers). Therefore, unless there is a history of malignancy, less rigorous follow-up CT is recommended than for older patients with nodules  $\leq 8$  mm.

### Nodules Suspicious For Malignancy

In some cases, benign nodules (granulomas, hamartomas) can be definitively diagnosed by CT imaging because they have distinctive patterns of calcification and fat (which are not found in malignancies).

Approximately 50% of incidentally detected nodules  $> 8$  mm are however malignant. Malignancy should be suspected in a patient with a prior history of cancer or in any case in which a nodule is increasing in size, and has certain morphologic characteristics considered indicative of malignancy; these include a spiculated outer margin, a hazy and indistinct margin, endobronchial extension, extension to pulmonary veins, and focal retraction of the adjacent pleura. Heterogeneous internal composition and associated necrosis are also concerning for malignancy.

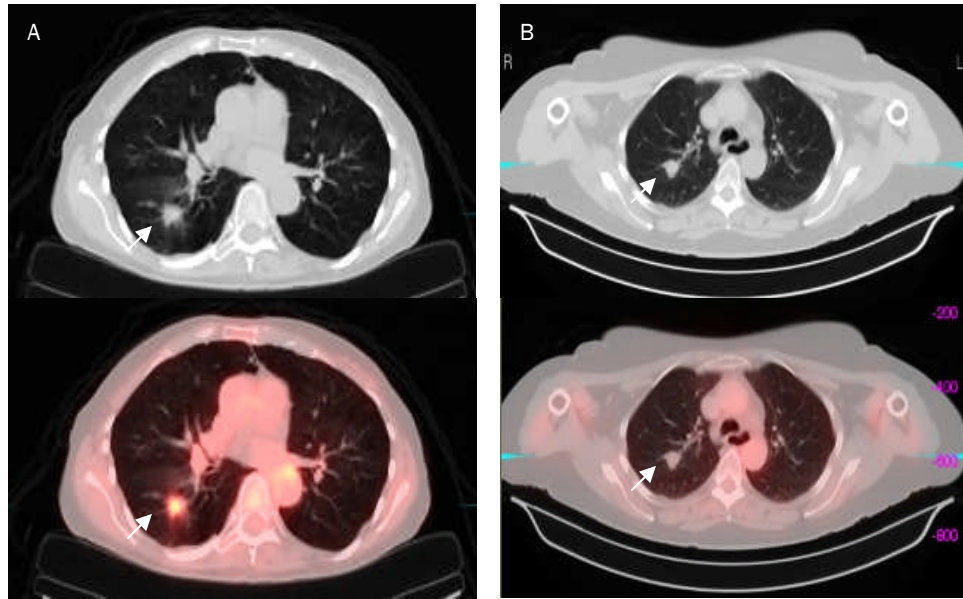
Malignant nodules are unfortunately not always easily distinguished from benign nodules on CT imaging and as many as 75% of nodules are characterized as indeterminate. Furthermore, 25% to 39% of malignant nodules are inaccurately classified as benign after x-ray and CT assessment of morphologic characteristics, including size, margins, contour, and internal characteristics. Further evaluation should therefore be considered for nodules  $> 8$  mm.

Nodules of any size in patients of any age with a history of cancer should have close follow up intervals because metastases demonstrate more rapid growth (Figure 2).

**Figure 1.**

(A) Transaxial CT and fused FDG PET/CT image showing a solitary pulmonary nodule with spiculated borders in right lower lobe. Hypermetabolism is present within this nodule. Findings consistent with malignancy.

(B) Solitary pulmonary nodule in a different patient in the right upper lobe. No hypermetabolism is present within this nodule. Findings consistent with a benign nodule.



## Modalities for Evaluation of Nodules

Once a nodule has been classified as suspicious by CT evaluation, it can be further evaluated with FDG-PET/CT, or invasively by percutaneous needle aspiration biopsy (PNAB) or video assisted thoroscopic surgery (VATS). Table 1 compares the advantages and disadvantages of these modalities.

As a non-invasive approach, FDG-PET/CT offers the advantage of more accurately characterizing potentially malignant nodes compared to CT, directing patients to further biopsy evaluation, while sparing patients from unnecessary invasive procedures.

## FDG-PET/CT Imaging

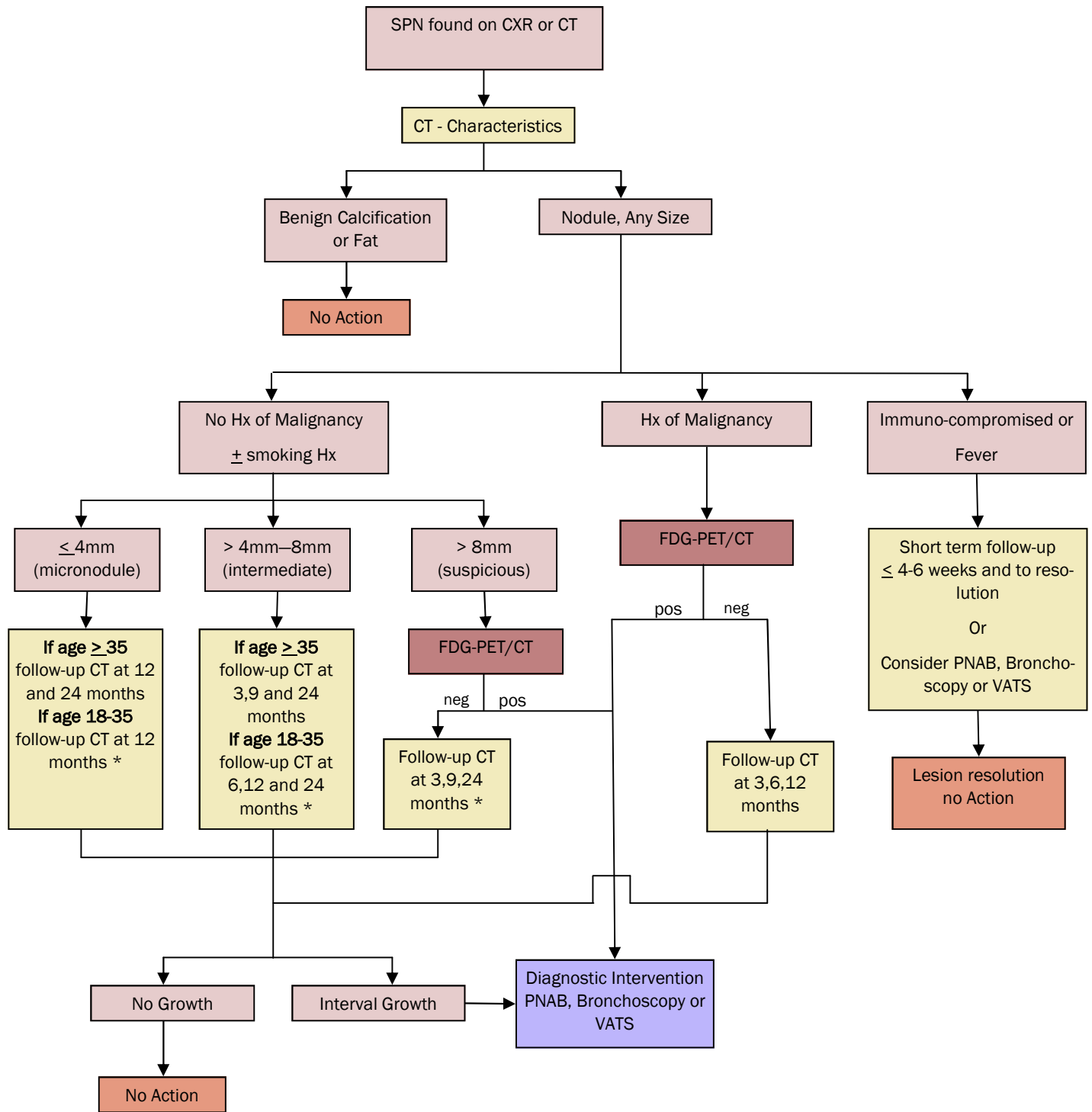
FDG-PET has been described as a better predictor of malignancy than clinical and morphologic criteria. Combining FDG-PET (metabolic imaging) with CT (anatomic imaging) as is now routinely performed with PET/CT, demonstrates even higher accuracy with excellent sensitivity (97%) and specificity (85%) in detecting malignant nodules > 8 mm (Figure 1).

FDG-PET scans are useful in identifying metabolically active nodules that require diagnostic biopsy, information that is particularly helpful in patients with significant co-morbidities.

In addition, FDG-PET is more accurate in detecting lymph node metastases in the thorax and provides the added advantage of whole-body staging for lung cancer. Up to 13% of patients with lung cancer have occult extrathoracic metastases detected on FDG-PET that conventional staging, including CT, missed (Figure 3).

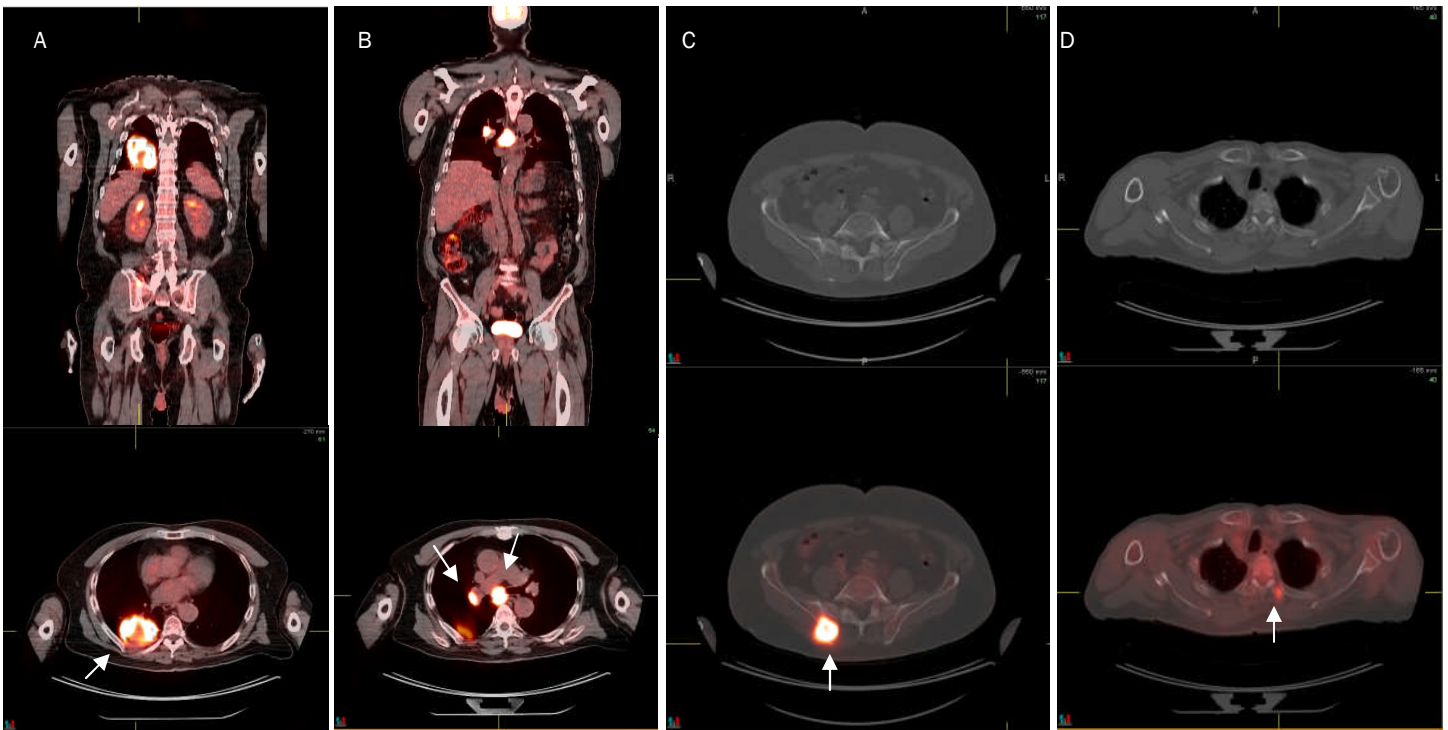
**Table 1. Comparison of modalities for evaluating pulmonary nodules**

Modality	Advantages	Disadvantages
PNAB	Histological diagnosis	- Low diagnostic yield for nodules < 8 mm - Minor pneumothorax, 20% - Significant pneumothorax, requiring chest tube, 1-2% - Minor hemoptysis, 2-5%
FDG-PET	- Accurate non-invasive evaluation - Whole body image detects extra-pulmonary tumors - Can stage known lung cancer	- Lower sensitivity for lesions < 8 mm - False positives from inflammation - False negatives from tumors with low metabolic rate
VATS (video assisted thoroscopic surgery)	Definitive histological diagnosis	- General anesthesia - Hospitalization, 1-3 days (longer in cases of prolonged air leak in 2-15%) - Arrhythmia, 3-4% - Bleeding, 4%



\* All Ages, longer follow-up for ground glass nodules

Figure 2. Guideline Algorithm for Evaluating Pulmonary Nodules



**Figure 3.** Lung cancer with regional nodal and distant osseous metastases (A–D). Coronal and axial FDG-PET/CT fused images (A, B) demonstrate a hypermetabolic cavitary lung mass in the right lower lobe (A) and additional lesions in ipsilateral hilum and mediastinal subcarina (B). Additional focus of hypermetabolism is seen in right ilium (C) and corresponds to lesion on CT. Axial images (D) show hypermetabolism in the left T3 vertebral pedicle without osseous changes on CT.

Certain tumors such as carcinoid, bronchioloalveolar cell carcinoma, and well differentiated adenocarcinoma demonstrate relatively low metabolic activity and are, therefore, less consistently detected with FDG-PET. However, most of these tumors have features on CT that are suspicious for malignancy that would warrant further diagnostic evaluation.

Inflammatory diseases may also appear positive on FDG-PET scans, resulting in false positive findings for cancer. On occasion, a nodule due to mycobacterial or fungal disease, sarcoidosis or organizing pneumonia can mimic a neoplastic pulmonary nodule.

## Multiple Pulmonary Nodules

The evaluation of multiple pulmonary nodules can be limited by potential false-positive findings on FDG-PET. Increased FDG activity has been demonstrated in instances of active granulomatous disease, such as tuberculosis, fungal disease, and sarcoidosis, as well as other inflammatory processes, such as rheumatoid nodules.

CT in combination with FDG-PET aids in the evaluation of multiple pulmonary nodules. In addition to the shapes, borders, and densities of the nodules, the distribution of the nodules can provide important clues to their etiology.

## Choice of Strategy for the Indeterminate or Suspicious Nodule

Based on the literature and on cost-effectiveness analysis, the preferred approach to patients with indeterminate or suspicious nodules favors FDG-PET/CT scanning as part of the diagnostic evaluation. FDG-PET/CT scanning allows more precise risk stratification. In particular, for older patients with concurrent medical illnesses, where the surgical risk may be significantly increased, avoiding unnecessary surgery is important. If the FDG-PET scan is negative, a strategy of serial CT scanning follow-up is justified. Similarly, a positive FDG-PET scan justifies the risk associated with surgery because malignancy is likely.

## References

P. Cronin, B. A. Dwamena, A. M. Kelly, and R. C. Carlos  
**Solitary Pulmonary Nodules: Meta-analytic Comparison of Cross-sectional Imaging Modalities for Diagnosis of Malignancy** Radiology, March 1, 2008; 246(3): 772 - 782.

S. K. Kim, M. Allen-Auerbach, J. Goldin, B. J. Fueger, M. Dahlbom, M. Brown, J. Czernin, and C. Schiepers  
**Accuracy of PET/CT in Characterization of Solitary Pulmonary Lesions** J. Nucl. Med., February 1, 2007; 48(2): 214 - 220.

MacMahon, H, Austin, JH, Gamsu, G, Herold, CJ, Jett, JR, Naidich, DP, Patz, EF, Jr. and Swensen, SJ.  
**Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society.** Radiology 2005 237: 395-400

Gould, MK, Sanders, GD, Barnett, PG, Rydzak, CE , et al.  
**Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules.** Ann Intern Med 2003 138: 724-35

M. K. Gould, C. C. Maclean, W. G. Kushner, C. E. Rydzak, and D. K. Owens  
**Accuracy of Positron Emission Tomography for Diagnosis of Pulmonary Nodules and Mass Lesions: A Meta-analysis** JAMA, February 21, 2001; 285(7): 914 - 924.

## Scheduling

FDG-PET/CT may be ordered by telephone at 520.321.4057 in Tucson or 928.314.4800 in Yuma.

## For Further Information

For further questions, please contact:

Fabio Almeida MD  
Medical Director  
Southwest PET/CT Institute, Tucson-Yuma  
520.321.4057

