Imaging Evaluation of the Solitary Pulmonary Nodule

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Doctor of Medicine

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Dedication

To my husband, Dane, for his loving support and guidance throughout my education, and during the research and writing of this thesis.
Acknowledgements

Dane Van Tassel, BS, BSHS, Michael B. Gotway, MD, Ronald L. Korn, MD, PhD contributed to this thesis and are listed as co-authors when in the published version of this document.
Abstract
An estimated 150,000 solitary pulmonary nodules (SPNs) are identified at chest radiography each year, making it important for physicians to understand how to characterize them and evaluate patients for potential malignancy. We performed an extensive literature search to identify risk factors, characteristics of SPNs, and available technologies used to identify and evaluate these nodules through a comprehensive literature search. Additionally, we present evidence-based management schemes for incidentally identified nodules. CONCLUSIONS: A number of features visible at thoracic CT are useful for determining whether an SPN is benign or malignant. FDG PET/CT plays an important role in the diagnosis and management of lung cancer and is an increasingly valuable tool for the characterization and management of SPNs. Unlike CT and MRI imaging, PET provides metabolic activity of a nodule. The information provided by PET/CT imaging allows for both morphological and anatomical characteristics as well as physiological data in the form of metabolism within the nodule itself. The information gained from PET is extremely useful for directing patient management and may obviate the need for invasive diagnostic procedures.
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Introduction

Solitary pulmonary nodules represent a diverse range of benign and malignant lesions (Table 1). The Fleischner Society (1) defines a solitary pulmonary nodule (SPN) as a rounded opacity, circumscribed or poorly defined, measuring up to 3 cm in diameter, completely surrounded by lung. In the most restrictive definition, SPNs are unassociated with atelectasis, hilar enlargement, or pleural effusion (2, 3). Opacities larger than 3 cm in diameter are referred to as masses to reflect to high rate of malignancy with lesions of this size (2, 4).

The prevalence of SPNs at chest radiography has been estimated at 1 in 500 chest radiographs (2, 3). Nodules are even more commonly detected at thoracic CT, and the problem of the incidental detection of pulmonary nodule is increasing due to the higher sensitivity of thoracic CT compared with chest radiography, as well as the increasing utilization of thoracic CT (5). It is critically important for physicians to have a firm understanding of how to integrate clinical, laboratory, and imaging data to develop an appropriate approach to the management of an SPN (3). Therefore, the goal of this review is to discuss the available technologies and recent advances for evaluation and follow up of incidentally found SPNs as well as some
discussion on the management strategies as they relate to available resources for imaging and patient risk factors.
Table 1: Solitary pulmonary nodules: common etiologies (2)

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Benign</th>
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<tr>
<td>Adenocarcinoma</td>
<td>Amyloidoma</td>
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<td>Bronchogenic carcinoma</td>
<td>Arteriovenous malformation</td>
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<td>Large cell carcinoma</td>
<td>Ascariasis</td>
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<td>Metastatic lesions (breast, head, neck, etc.)</td>
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<td>Pulmonary carcinoid</td>
<td>Atypical mycobacteria</td>
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<td>Small cell carcinoma</td>
<td>Bacterial abscess</td>
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<td>Squamous cell carcinoma</td>
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<td>Blastomycosis</td>
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<td>Intrapulmonary lymph nodes</td>
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<td>Mucoid impaction</td>
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<td>Pneumocystis carinii</td>
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<td>Pseudotumor (loculated fluid)</td>
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<td>Pulmonary infarct</td>
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<td>Pulmonary varix</td>
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<td></td>
<td>Rheumatoid nodule</td>
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<td>Rounded atelectasis</td>
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<td>Tuberculosis</td>
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<td>Wegener's granulomatosis</td>
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Methods

We reviewed relevant studies regarding imaging technologies and their use in evaluation and management of SPNs. Appropriate studies were identified by literature search using the PubMed and MEDLINE databases. Key Terms: solitary pulmonary nodule, coin lesion, incidental nodule, CT, PET/CT, FDG-PET. Our end points of concern were risk factors, imaging techniques of SPNs, and the evaluation and management of SPNs in current practice.
Clinical Characteristics Impacting the Likelihood of Malignancy within an SPN

A number of clinical factors impact the likelihood of malignancy with in an SPN, but the most important of these are the patient’s age, history of smoking, and history of prior malignancy (2).

Patient Age

As a patient’s age increases, the risk for malignancy within an SPN increases. Multiple studies examining the correlation between age and malignancy have found that that the risk for malignancy within an SPN is approximately double for patients over the age of 50 compared with patients younger than the age of 50 (6). Unfortunately, it is difficult to identify an age below which primary pulmonary malignancy need not be considered within the differential diagnosis of SPNs discovered at chest radiography. Some of this difficulty arises from the fact that a history of smoking strongly impacts the likelihood of malignancy within an SPN (see below). Furthermore, certain conditions that preferentially affect younger patients- such as tracheobronchial papillomatosis (Figure 1)- may increase the likelihood of malignancy within an SPN. Finally, uncommon primary pulmonary malignancies typically affect patients at a younger age than
bronchogenic carcinoma—such malignancies include carcinoid tumors and pulmonary blastomas. Nevertheless, the prevalence of malignancy within an SPN in a non-smoking patient without a history of malignancy, under the age of 35, is less than 1% (7). This prevalence of malignancy is low enough that most SPNs in such patients may be approached under the assumption that primary pulmonary malignancy is a very unlikely cause for the nodule.
Figure 1: Malignant solitary pulmonary nodule in a 26-year-old patient with tracheobronchial papillomatosis: squamous cell carcinoma. Frontal chest radiograph shows a 2.9 cm nodule (arrow) in the right upper lobe. Biopsy showed squamous cell carcinoma. The right paratracheal region is widened, representing lymphadenopathy.
**Smoking History**

Cigarette smoking is the most important causative factor in the development of bronchogenic malignancies, and therefore strongly influences the likelihood of malignancy in an SPNs (8). The risk of for the development of bronchogenic carcinoma increases with the quantity of cigarette consumption and the duration of smoking (8), but, the lack of a smoking history does not guarantee that an SPN does not harbor malignancy. Other risk factors for bronchogenic carcinoma, which will increase the likelihood of malignancy in an SPN, include occupational or environmental exposures such as asbestos and radon, certain metals (cadmium, chromium, and arsenic), radiation, some organic chemicals, and pulmonary scars.

**History of Extrapulmonary Malignancy**

In an adult patient with a history of prior malignancy who presents with a new lung nodule at imaging, the physician must consider the possibility that the new nodule represents a primary bronchogenic malignancy, a solitary metastases (Figure 2), or a benign finding. The frequency of each of these etiologies varies with the age of the patient, smoking history, and the type of study (surgical versus population series). In a study of greater than 800 patients over a
period of 35 years, Cahan, et. al. (9) found that at least 63% of SPNs (500 of more than 800 patients) were due to primary lung malignancy, at least 25% (196 of more than 800 patients) of SPNs were the result of solitary metastases, and in only 11 of over 800 patients (1.4%) were the SPNs the result of benign lesions. The distribution of malignant versus benign lesions in this study (9), and other surgical studies, differs from data reported in population studies and reflects the bias intrinsic to studies based on surgical patient cohorts.
Figure 2: Malignant solitary pulmonary nodule in a 44-year-old patient with lower extremity malignant fibrous histiocytoma: solitary metastases. Axial thoracic CT shows a 2.5 cm nodule (arrow) in the subpleural right lung proven to represent a solitary metastasis from soft tissue sarcoma.
Of particular importance is the histopathology of the extrapulmonary malignancy. In a study of 149 adult patients with synchronous or metachronous extrapulmonary neoplasms and non-calcified SPNs 5-30 mm in size found at thoracic CT (10), the nodules in patients with primary carcinomas of the head/neck, bladder, esophagus, bile ducts, ovary, prostate, breast, cervix, and stomach were more likely to be the result of a new primary lung malignancy than pulmonary metastases. In contrast, the SPNs of patients with primary testicular carcinoma, melanoma, or sarcomas (Figure 2) are far more likely to harbor metastatic disease than bronchogenic carcinomas (10). No patient under the age of 44 had bronchogenic malignancy in this study, and 30 of 149 patients (20%) in this cohort had a benign SPNs. (10). The study of Cahan, et. al. (9) showed a similar SPN etiology dependence on the histopathology of the extrapulmonary lesion.

When accounting for numerous factors impacting the likelihood of malignancy in a nodule, it has been estimated that the probability of malignancy in an SPN in an adult patient discovered at chest radiography is about 40% (11). The task of the physician caring for
patients with SPNs is to use clinical, laboratory, and imaging information to modify this probability to a sufficiently low likelihood that the lesion may be safely followed or to a sufficiently high likelihood that intervention is warranted.
Chest Radiographic and Thoracic CT Features of Malignant and Benign Solitary Pulmonary Nodules

Likelihood Ratios

A number of morphological features of SPNs visible at chest radiography and thoracic CT influence the likelihood that an SPN is benign or malignant (Table 2). These features have variable predictive value. The process by which these features are integrated into an overall assessment of the likelihood of malignancy is referred to as Bayesian analysis, and this process underlies the core of SPN management.
**Table 2:** Chest Radiographic and Thoracic CT Morphologic Abnormalities Associated with Malignancy in an SPN

<table>
<thead>
<tr>
<th>Favors Malignancy</th>
<th>Favors Benign</th>
<th>Little Influence On Presence of Malignancy</th>
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<tr>
<td>Large Nodule Size</td>
<td>Small Nodule Size</td>
<td>Pleural Tail</td>
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<tr>
<td>Spiculated or Lobulated Border</td>
<td>Smooth Border</td>
<td>Nodule Location</td>
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<td>“Notch” Sign, Corona Maligna</td>
<td>Round, Oval, or Tubular Shape</td>
<td>Air-Crescent</td>
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<td>Irregular Shape</td>
<td>Lack of Growth for &gt; 2 Years</td>
<td>Feeding Vessel Sign</td>
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<td>Thick-walled Cavitation “Vascular Convergence” Sign</td>
<td>Satellite Nodules</td>
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<td>Air Bronchogram</td>
<td>Calcification</td>
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<td>Ground-glass or Part-Solid Attenuation</td>
<td>Fat or Water Attenuation</td>
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<td>Positive Contrast Enhancement on CT or MRI</td>
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<td>Hypermetabolism on FDG-PET</td>
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The ability of clinical, laboratory, and imaging features to impact the likelihood of a benign or malignant SPN diagnosis is often quantified in terms of likelihood ratios (LRs); LR’s for individual imaging features of SPNs have been published (7, 12). The likelihood ratios for various clinical factors, along with imaging features of SPNs, can be combined to provide an overall assessment of the likelihood of malignancy for a given SPN (2). For example, the likelihood ratio for an upper lobe location for an SPN has been reported as 1.22 in one publication (7)- this value indicates a slightly increased likelihood of malignancy when an SPN is found in the upper lobes as opposed to other locations. Using the previously asserted baseline prevalence of malignancy within an SPN discovered at chest radiography of 40%, the prevalence of malignancy for an upper lobe SPN increases slightly to 49%. In contrast, the likelihood ratio for lack of significant tracer utilization at FDG PET is 0.06 (12). In this example, an SPN discovered at chest radiography subsequently shown to possess no significant metabolic activity at FDG PET will have a probability of carcinoma of only 2.4%.
Web-based calculators (www.chestx-ray.com) are available to automate the use of LRs in determining the probability of carcinoma in an SPN. Users simply input the information regarding certain clinical factors, such as age and smoking history, and several relevant radiologic features of the SPN, and a likelihood of malignancy within the SPN is instantaneously calculated.

Some of the SPN morphologies visible chest radiography and thoracic CT that have the greatest utility for predicting a benign or malignant etiology for an SPN will be reviewed below. The role of FDG-PET in the evaluation of the SPN has grown enormously in recent years and FDG-PET has been proven to be a very powerful tool for nodule evaluation. Therefore, FDG-PET will be discussed separately in detail subsequently.
Thoracic Imaging Features that Predict a Malignant SPN Etiology

A host of imaging features has been evaluated for their ability to suggest whether or not an SPN found at chest radiography or thoracic CT is malignant (Table 2). Some of the more important predictors of malignancy within an SPN include the appearance of the edge (margin or contour) of the nodule, the shape of the nodule, nodule size, nodule attenuation at thoracic CT, and hypermetabolism at FDG-PET.

Nodule Edge / Margin / Contour

The edges (also often referred to as the margin, border, or contour) of a nodule describe the interface of the nodule with adjacent lung, and may be characterized as circumscribed (smooth), lobulated, spiculated, or irregular. A smooth, or circumscribed, nodule margin is present when the nodule edges are easily traced and the interface with adjacent lung is sharply demarcated (Figure 3A). Circumscribed nodule margins are typical of benign lesions and are uncommonly present with primary lung malignancies. However, the predictive value of a smooth nodule margin is lowered by the fact that metastatic pulmonary nodules often present in this manner. A nodule is described as lobulated when an undulating contour is present (Figure 3B) - this
nodule morphology is commonly seen with malignancy, although benign lesions may occasionally present in this fashion. A nodule is described as having a *spiculated* border when irregular, linear “spike-like” points radiate from the nodule into the surrounding lung parenchyma (Figure 3C). Unlike circumscribed nodule borders, the edges of a spiculated nodule are not easily traced. A spiculated nodule edge is a strong predictor of malignancy and is a common manifestation of bronchogenic carcinoma (Figures 3C, 4) (2).
**Figure 3:** Nodule edge (aka, border, margin) characteristics at CT: circumscribed / well-defined edges (A) in a pulmonary infectious granuloma (arrow), lobulated edges in pulmonary adenocarcinoma (arrow) (B), and spiculated edges (C) in pulmonary adenocarcinoma (arrow). Arrowheads in (B) show the concavity at the site of the “notch” - note the presence of a pulmonary vessel entering this region, typical of the “notch” sign. The posteromedial portion of this lesion shows a spiculated edge.
Figure 4: Nodule edge (aka, border, margin) characteristics at chest radiography: spiculated edge. Coned view from a chest radiograph in a 60-year-old man shows spiculated left upper lobe nodule (arrow) subsequently shown to represent adenocarcinoma.
The margin of a nodule may be described as *irregular* when the interface the nodule creates with the lung is not properly described as circumscribed, lobulated, or spiculated.

**Nodule Shape**

Nodule *shapes* may be described as *round, oval, notched,* or *irregular.* The nodule shape descriptors *round* and *oval* carry little predictive value as both benign and malignant SPNs may present with these shapes. The *notched* shape, however, is a fairly strong predictor of malignancy within an SPN. The notched nodule shape refers to a concavity within an otherwise generally spherical nodule, usually associated with a bronchus or blood vessel entering the nodule at or near the site of the concavity (Figure 3B). This shape is fairly similar to the “lobulated” nodule border characteristic, and both descriptors imply a similar pathophysiological process—differential growth of a nodule, which is typical of malignancy. Pulmonary malignancies, particularly bronchogenic carcinomas, grow in an asymmetric fashion, which results in variable convexities and concavities along the surface of a nodule, outwardly manifesting as a lobulated edge or notched shape.
Nodule Size

As a general rule, the rate of malignancy within a nodule rises as nodule size increases (2). Unfortunately, there is no lower size limit at which malignancy can be confidently excluded. In the study by Ginsberg, et. al., (13) among 254 patients who underwent video-assisted thoracoscopic resection of a single pulmonary nodule, 114 nodules were benign and 140 were malignant. In this study, a total of 685 nodules were resected, and 36% of these nodules measuring < 1 cm were malignant. Nodules >1 cm but <3 cm were more likely to be malignant than nodules <1 cm, but there is no “safe limit” below which malignancy can be excluded within a pulmonary nodule, particularly in patients with current or previous malignancy. There is certainly a trend which favors a benign diagnosis for smaller nodules, but nodule size alone is an insufficiently sensitive discriminator between benign and malignant nodules (Figure 5).
Figure 5: Malignant subcentimeter pulmonary nodule in a 65-year-old patient. Initial CT image (A) shows a small pulmonary nodule (arrow) measuring 5 mm (arrow). Follow up CT 18 months later (B) shows that the lesion (arrow) has grown. Resection subsequently proved the nodule was due to adenocarcinoma.
**Nodule Attenuation at Thoracic CT**

The *density*, or *attenuation*, of a nodule at CT has been correlated with the presence of certain types of primary pulmonary malignancies, particularly bronchioloalveolar carcinoma (BAC). It has been noted that pure ground-glass opacity nodules (often referred to as *subsolid* nodules—nodules in which the underlying pulmonary architecture is visible through the lesion) correlate histopathologically with the replacement growth pattern typical of BAC (Figures 6 and 7). When ground-glass opacity nodules begin to show solid components, increasingly advanced histopathological features of malignancy are often present (Figure 6B). The ground-glass opacity appearance of a focal nodule at thoracic CT is not completely specific for BAC as areas of focal fibrosis and atypical adenomatous hyperplasia may present in this fashion (14).
**Figure 6**: Ground-glass attenuation SPN on thoracic CT: bronchioloalveolar carcinoma. Axial thoracic CT shows 2 examples of ground-glass opacity nodules. The nodule (arrow) in (A) was proven pure bronchioloalveolar carcinoma. The large nodule (arrows) in (B) was adenocarcinoma with bronchioloalveolar features. In (A), and the anterior portion of (B), note that vessels and pulmonary architecture can be seen through the area of increased attenuation—this is the definition of “ground-glass opacity.” In (B), note the increased attenuation posteriorly (arrowheads)—such features predict advancing histopathological evidence of malignancy, such as invasive adenocarcinoma.
Figure 7: Ground-glass attenuation SPN on thoracic CT: bronchioloalveolar carcinoma. Thoracic CT in 2003 (A) shows a subcentimeter ground-glass attenuation nodule (arrow) in the right upper lobe. Follow up CT in 2008 (B) shows that the nodule (arrow) has grown. Subsequent resection showed bronchioloalveolar carcinoma.
A number of other morphological features of SPNs occasionally visible at chest radiography and usually readily appreciable with CT have been associated with malignancy (Table 2). Some of these features include the presence of an air bronchogram within an SPN (Figure 8A) and the presence of non-enlarged vessels entering an SPN (the “convergence” sign; Figure 8B), among others.
Figure 8: CT features of SPNs associated with malignancy: air bronchogram (arrow) within pulmonary adenocarcinoma (A) and the “convergence” sign in primary pulmonary malignancy (B). Note the non-enlarged pulmonary vessels (arrowheads) converging on the small nodule (arrow) in (B); compare with arteriovenous malformation in Figure 10.
Thoracic Imaging Features that Predict a Benign SPN Etiology

Certain morphological features of an SPN found at chest radiography or thoracic CT are associated with benign diagnoses. These features include the feeding artery and draining vein of an arteriovenous malformation (Figures 9 and 10), rounded atelectasis (Figure 11), mucous plugging (Figure 12), certain patterns of calcification within a nodule, visible fat within a nodule, lack of nodule enhancement at thoracic CT or MR, nodule growth characteristics, and lack of significant tracer utilization at FDG-PET. The more important and commonly encountered morphological features that allow an SPN discovered at thoracic imaging to be diagnosed as benign will be reviewed below.
Figure 9: Pulmonary arteriovenous malformation: chest radiography. Frontal (A) and lateral (B) chest radiography shows a right lung nodule (arrow) with a tubular opacity (arrowheads) leading from the right pulmonary artery to the lesion.
Figure 10: Pulmonary arteriovenous malformation: thoracic CT. Axial thoracic CT shows a peripheral left lung nodule (arrowhead) with enlarged feeding artery and draining vein (arrows). Compare with convergence sign for a malignant pulmonary nodule in Figure 7B. Note in the case of pulmonary AVM, the vessels associated with the nodule should be enlarged.
Figure 11: Rounded atelectasis: chest radiography and thoracic CT. Frontal (A) and lateral (B) chest radiographs show volume loss and pleural abnormality in the left thorax, with an oblong nodule (arrow) in the left lung. While these findings raise the possibility of rounded atelectasis, they are insufficiently specific to exclude malignancy. Thoracic CT displayed in lung (C) and soft tissue (D) windows shows the left lung opacity is associated with vessels (double arrowheads) spiraling into the lesion (arrow), representing the “comet tail” sign. Volume loss (note posterior displacement of left major fissure, just
anterior to arrowheads in C) is also present. The lesion (arrow) obeys other features expected with rounded atelectasis, such as a homogenous appearance and contact with abnormal pleura (single arrowhead in D).
Figure 12: Bronchial atresia: chest radiography and thoracic CT. Frontal chest radiograph (A) shows a non-specific nodule (arrows) projected through the left aspect of the mediastinum. Thoracic CT (B, C, and D) shows the nodular opacity (arrow in B) and, slightly more distally (C), has a branching configuration (arrowheads in C). Note the extensive hyperlucency throughout the left lower lobe, representing post-obstructive air trapping; compare with the normal appearing right lower lobe. The air trapping (arrowheads) is shown to advantage in the volume-rendered thoracic CT image (D).
Patterns of Calcification within an SPN

Calcification within an SPN generally indicates that an SPN is benign, and is typically occurs within nodules resulting from granulomatous infections or hamartomas. The mere presence of calcium within an SPN is a fairly strong indicator that the SPN is benign. In 1957, O'Keefe (15) noted that, in 72 resected malignant SPNs, only 1.4% of malignant SPNs had calcification visible on chest radiography. In contrast, 34% of resected benign SPNs showed calcification at chest radiography (15). This work, and the work of subsequent investigators, has repeatedly shown that the presence of calcification within a nodule predicts that the SPN is benign, but does not absolutely exclude malignancy. Calcification within bronchogenic malignancies is typically rarely visible at chest radiography (Figure 13A), but can occasionally be appreciated with thoracic CT (Figure 13B). Metastatic lung nodules (Figure 14) may also calcify, particularly in patients with thyroid carcinoma, osteosarcoma, chondrosarcoma, and mucinous tumors, such as some ovarian malignancies.
Figure 13: Calcification within primary bronchogenic carcinoma: chest radiography and thoracic CT. Frontal chest radiograph (A) shows a poorly defined right upper lobe nodule (arrow). Calcification is not discretely visible within the lesion. Thoracic CT (B) shows that the nodule (arrow) contains some amorphous calcification (arrowhead). The lesion was proven adenocarcinoma at resection.
Figure 14: Calcification within metastatic lung nodules (arrows): thyroid carcinoma (A), osteosarcoma (B), and ovarian carcinoma (C).
Ultimately the pattern of calcification within an SPN is more useful than the mere presence of calcification within an SPN for determining if a lesion is benign. Indeed, the pattern of calcification, rather than the mere presence or absence, is one of the two primary non-invasive criteria which allow an SPN to be considered absolutely benign (the other is lack of growth over a period of time; see below) (2). Four benign patterns of SPN calcification are recognized: diffuse calcification, central calcification, laminar (“target”) calcification, and chondroid (“popcorn”) calcification (Figures 15-17, 18C) (2). When calcification occurs within a malignant primary pulmonary neoplasm, the calcification is often stippled (tiny, punctuate foci of calcium) or eccentric. The latter pattern is thought to result from a malignant nodule arising adjacent to and engulfing a calcified granuloma.
Figure 15: Nodule calcification patterns.
Figure 16: Benign patterns of calcification: diffuse calcification, central calcification, and laminar (“target”) calcification patterns. Frontal chest radiograph (A) and thoracic CT (B) in a patient with a post-infectious granuloma shows diffuse calcification within a nodule (arrows). Note that the nodule (arrow) appears denser than the rib on the chest radiograph (A). Frontal chest radiography (C) and thoracic CT (D) in a patient with a post-infectious granuloma shows central calcification within a pulmonary nodule (arrows). The nodule was thought to be the result of histoplasmosis. Frontal chest radiography (E) and thoracic CT (F) in a patient with a nodule (arrow) of undetermined etiology shows a laminar (“target”) pattern of calcification.
Figure 17: Calcification within a giant pulmonary hamartoma: chest radiography and thoracic CT. Coned digital image (A) shows a right lower lobe mass with punctuate foci of calcification. Thoracic CT (B) shows irregular, nodular foci of calcification throughout the lesion.
Figure 18: Pulmonary hamartomas on thoracic CT: characteristic patterns. Thoracic CT shows fat (A and B) within pulmonary nodules (arrows) in two separate patients- note the low attenuation. Thoracic CT in a third patient (C) with hamartoma shows a nodule (arrow) with a chondroid, or “popcorn,” pattern of calcification characteristic of cartilage within the lesion.
Assessing an SPN for calcification is a powerful means to determine whether or not further evaluation is required for a nodule. Nevertheless, a few caveats must be borne in mind:

1. When attempting to discern the pattern of SPN calcification, if a significant soft tissue component is present, caution is warranted (Figure 13B). How much non-calcified soft tissue is “allowable” to still consider a nodule as benign is debatable, but the more visible the non-calcified component, the more the nodule should be regarded as indeterminate;

2. Calcification patterns within nodule are not reliable for distinguishing between benign and malignant nodules when patients have extrapulmonary malignancies that are known to calcify or ossify (Figure 14), and;

3. Care should be taken when considering a nodule calcified at chest radiography.

Regarding the latter, Berger, et. al. (16) evaluated the ability of 14 board-certified radiologists to determine whether or not an SPN was calcified at chest radiography and found that the positive predictive value for a “definitely calcified” assessment of a nodule was 93%.
Because nodules considered calcified at chest radiography generally are not evaluated further, the implication of this work is that nearly 7% of patients with non-calcified SPNs could be incorrectly classified as calcified at chest radiography and inappropriately dismissed without further evaluation. Recalling the baseline prevalence of malignancy in an SPN of 40% discussed previously, it is therefore conceivable that 3-4% of malignant SPNs discovered at chest radiography could be incorrectly dismissed as calcified and therefore benign.

There are few guidelines for determining whether or not a nodule is calcified. One useful criterion, however, is nodule size: the smaller the nodule, the more likely it is calcified. This relationship exists because smaller nodules require sufficient density to achieve the level of contrast resolution needed to allow them to be visible at chest radiography. Nodules containing calcium are intrinsically denser than non-calcified nodules; therefore, for a small nodule to be visible at chest radiography, it likely contains calcium. In a study evaluating this concept, Ketai, et. al. (17) found that nodules <7 mm in diameter at chest radiography were very likely to be calcified, particularly if the
nodule appeared to be as dense as or denser than the adjacent rib (Figure 16A). These data correlate fairly well with the notion that primary bronchogenic carcinomas, which are typically non-calcified, are not visible on chest radiographs when <1 cm in size (2, 17, 18).

*Fat within a Nodule: Hamartoma*

Hamartomas are mesenchymal lesions that contain variable degrees of connective tissue elements, such as smooth muscle, myxomatous tissue, epithelial tissue, adipose tissue, fibrous tissue, and cartilage. Hamartoma is one of the more common causes of an SPN and more than 90% of hamartomas present as a peripheral SPN. Hamartomas present as round, circumscribed or mildly lobulated lesions that range from 1-4 cm in diameter, but occasionally may be much larger (Figure 18).

Hamartomas may manifest as a non-specific SPN, but calcification may occur in 5-50% of lesions on CT (19). Occasionally the pattern of calcification within a hamartoma will reflect the presence of cartilage within the lesion—so-called “popcorn,” or chondroid, calcification (Figures 17B and 18C). Hamartomas may also contain
adipose tissue and may show macroscopic evidence of fat at CT, allowing a specific diagnosis (Figures 18A and B) (19).

**Nodule Enhancement at Thoracic CT or MR**

Pulmonary malignancies are vascularized lesions that typically show contrast enhancement at enhanced thoracic CT or MR examinations. While the sensitivity of contrast enhancement at thoracic CT for the detection of malignancy is as high as 98% (2, 20), the specificity for this finding is only 58% because benign nodules, such as active granulomas rounded atelectasis, focal pneumonia, and hamartomas, may enhance following contrast administration. Although the presence of contrast enhancement does not reliably discriminate between benign and malignant lesions, the lack of contrast enhancement at thoracic CT or MR is a strong indicator that a pulmonary nodule is benign. In a multicenter study, Swensen, et. al., (20) showed, when using a specific contrast-enhanced thoracic CT protocol, that nodule enhancement of ≤15 HU carries a negative predictive value of 96% for malignancy.
Nodule Growth Characteristics

Malignant pulmonary nodules will show growth on serial imaging studies, although the rate of growth may vary widely depending on the type of malignancy. The detection of growth within a nodule is one of the main reasons comparison chest radiographs are of paramount importance when assessing nodules—every effort should always be made to obtain prior radiographs for this purpose (2).

The presence of growth is often taken as an indicator of the potential for malignancy within an SPN, and thus the demonstration of growth serves as an endpoint for nodule surveillance with chest radiography or thoracic CT. Similarly lack of growth is often used as an indicator that a pulmonary nodule is benign—clear demonstration that a nodule has shown no growth for a period of 2 years or more has traditionally been considered an absolute indicator that the lesion is benign (2). This criterion for a benign nodule has been questioned in recent years on the basis that the original data supporting this approach are insufficient (2, 21). Nevertheless, 2-year nodule stability at imaging is still widely regarded as an absolute indication that a nodule is benign (2, 7, 16, 19), but with several caveats:
1. To determine if a nodule is truly stable, it must be reasonably well seen. This statement does not indicate that only CT is sufficient for determining nodule stability, although one of the many advantages of thoracic CT for nodule assessment is that the margins of a nodule are far better appreciated with CT than chest radiography in many patients;

2. Accurate determination of growth of small nodules (<1 cm) on thoracic CT can be difficult. In particular, caution regarding confident assessments of lack of growth for small nodules is warranted. Automated software calculation of nodule volume may provide an improved approach to the assessment of such small nodules (7, 19) (Figure 19), and;

3. Ground-glass opacity nodules detected at thoracic CT may reflect slow-growing neoplasms, such as BAC (Figures 6 and 7). Therefore, some investigators have advocated that such nodules show no growth for at least 5 years before dismissing them as benign (2, 14).
Figure 19: Serial growth of a small pulmonary nodule using automated nodule volumetry. Initial three-dimensional image (A) of nodule results in a volume calculation of 99 mm$^3$. Ninety days later, follow up CT was performed and nodule (B) volume had increased to 138 mm$^3$, representing a 28% increase in volume (Image courtesy of GE Medical Systems, Milwaukee, WI).
In recent years, further refinements in software now allow automated calculation of the *volume* of a nodule at serial thoracic CT examinations (Figure 19). Preliminary studies suggest that the use of such software provides a more robust determination of nodule size, with less interobserver variability among serial CT examinations when assessing for nodule growth compared with manual measurements (7, 19).

When an SPN is detected at chest radiography or thoracic CT and prior imaging studies are available, determination of the nodule growth rate can provide an indication regarding the nodule’s malignant potential. To make this determination, the nodules’ *doubling time* can be calculated. The doubling time of a nodule is the time required for the nodule to double in *volume*, not *diameter*, and is governed by the formula for the volume of a sphere- $4/3\pi r^3$. An increase in the diameter of a nodule by 26% reflects a doubling of the volume of a nodule; when a nodule has doubled in diameter, its volume has increased 8-fold. In general, pulmonary malignancies (Figures 5 and 20) will double in volume between 30 and 480 days. Lesions that grow faster than a doubling time of 30 days are often infectious in nature,
and doubling times longer than 480 days are also more typical of benign lesions. However, there are exceptions to these rules. Rarely some cancers, particularly small cell carcinomas, may double in volume in less than 30 days. On the other end of the spectrum, some pulmonary malignancies, particularly BACs, may grow very slowly (Figure 7); doubling times as long as 1486 days have been noted. In Figure 7, the small BAC grew from 4 mm to 9 mm over a period of 1827 days, yielding a doubling time of 521 days. For this reason, slow doubling times cannot be regarded as an absolute indicator of a benign nodule.
**Figure 20:** Growth of a malignant SPN on serial chest radiography: metastatic colorectal carcinoma. Three serial chest radiographs (A-C) show progressive growth in an SPN (arrows) over a period of 400 days. The calculated doubling time was 133 days. Biopsy showed colorectal carcinoma.
**PET and PET/CT Technology**

Positron emission tomography (PET) has a well-established role in the diagnosis and management of lung malignancy. Unlike anatomic imaging methods, which rely on assessment of the morphologic characteristics of pulmonary opacities, PET imaging with radioactive tracers allows for the identification of metabolic activity within the lesion to indicate its aggressive potential. PET imaging exploits the detection of photons created as a result of the annihilation of a positively charged electron (positron) colliding with a nearby negatively charged electron, which produces two 511 keV photons emitted in near opposite directions. Photons that interact with the sophisticated crystal detectors at near identical times (less than 12 ns apart) are recorded and used to generate a tomographic image. PET detectors surround the patient and acquire data from all angles simultaneously. Although image quality with PET systems is generally superior to other nuclear medicine-based camera technologies, important photon interactions can cause image degradation and lead to artifacts in the final image that can either create or obscure a lesion. Such artifacts result from photon scatter, attenuation from tissue,
random coincidences, dead time, respiratory or body movement and noise (22, 23).

Of these processes, attenuation of photon activity is probably the factor that most affects image quality. Attenuation is a result of the absorption of either of the pair of emitted photons, resulting in loss of detection of the event source. Because the density of tissue changes along the projected pathway of emitted photons, true counts are lost and noise, artifact, and distortion results in a misrepresented image. Without the ability to rectify photon loss through attenuation correction, the activity within various body parts will be misrepresented in the final image. For example, without attenuation correction, the skin shows prominent activity due to a lack of attenuation at the body surface, while areas of low attenuation, such as the lungs, show diffusely increased activity (Figure 21). Correction of these distortions is important for detailed positional representation, and accurate quantization. Currently, the most common method of measuring count loss employs the use of CT scans built into a PET scanner (PET/CT) to provide accurate attenuation correction. Using PET/CT, attenuation maps are created from the density differences measured by CT. These maps are then used to add counts back to the
areas of PET showing high attenuation, such as beneath bone and deep
tissues, and to subtract counts in areas with low density, such as the
lung tissue (24) (Figure 21). By incorporating attenuation maps from
CT, the attenuation corrected PET images more accurately represent
true activity within the body. Due to the addition or subtraction of
counts, however, attenuation correction may result in increased or
decreased activity in a location of interest. As a result, a lesion found
to be suspicious on CT may not appear metabolically active on
attenuation-corrected PET (PETAC); however, when the non-
attenuation corrected PET (NACPET) images are examined, increased
metabolic activity will be seen. For this reason, review of both PETAC
and NACPET images can be useful for the interpretation of SPNs.

In addition to the accurate and rapid attenuation maps
generated by CT, PET/CT offers the advantage of image fusion. Thus,
the functional emission data from PET can be combined with the
anatomic information on CT to produce a fused image. As a result, a
more accurate assessment of a lesion’s true malignant character can be
performed than using either system alone (36).
Figure 21: The importance of viewing the non attenuation corrected (No AC) images on FDG PET/CT scans for pulmonary nodules. Note that the larger, but not smaller of the two pulmonary nodules is hypermetabolic on the axial slice PET with attenuation correction (AC: arrow). The corresponding No AC image (D) show increased activity in the smaller lesion (arrowhead) as well. Both lesions turned out to be lung malignancy.
Radioisotopes used in PET imaging

The most commonly used radionuclide for thoracic PET is radioactive fluorine (\(^{18}\text{F}\)) linked to deoxyglucose, resulting in the 2-(fluorine-18) fluoro-2-deoxy-D-glucose (FDG) molecule. FDG is a glucose analog with a half-life of 110 minutes that is taken up by almost all tissues in proportion to tissue metabolic activity. FDG allows selective identification of malignant tissues because such tissues over-express the glucose transport protein (Glut TP), and Hexokinase II, and therefore accumulate relatively more radiolabeled tracer than normal tissues. FDG accumulates within metabolically active cells because the radiolabeled glucose analog is phosphorylated by Hexokinase II upon entering the cell, forming FDG-6-Phosphate (FDG-6-P) - a negatively charged molecule that becomes trapped within the cell. Because tumors grow more rapidly than normal tissue, malignancies will appear as foci of hypermetabolism, or radioactive “hot spots,” on FDG-PET images (25). Thoracic FDG-PET is most commonly used for lung cancer staging, surveillance for malignancy recurrence, and response to therapy for oncology patients, but has also gained widespread use for the evaluation of the SPN (2). One limitation of FDG is that it is also taken up in a variety of infectious
and inflammatory processes leading to a relatively high but clinically acceptable false positive rate. This limitation has resulted in the search for other PET radiopharmaceutical agents that are not taken up by such processes. One such agent is Fluorine-18 3’-Deoxy-3’-Fluorothymidine (F-18-FLT). This promising new radiopharmaceutical for oncologic imaging indirectly measures DNA synthesis or cellular proliferation through incorporation into the overactive pyrimidine salvage pathways in proliferating tissues. F-18-FLT has demonstrated increased specificity for tumor cells through lack of significant accumulation within inflammatory tissues, FDG (26).

Other PET radioisotopes, such as $^{11}$C, $^{13}$N, $^{15}$O are much more difficult to use in routine clinical practice because of their very short half-life, cellular metabolism and delivery demands. These isotopes are used mainly in research settings.

*Radiation Exposure with PET/CT*

Recently, the potential teratogenic and carcinogenic impact of radiation has been the focus of much scientific and journalistic debate. With the advances in radiology technologies, population exposure to radiation has exploded over the last two decades. Although controversial, it has been estimated that between 2-5% of all cancers in
the next 10-20 years could arise as a result of medical imaging (27),
and the International Commission on Radiological Protection (ICRP)
has estimated that the radiogenic fatal cancer risk for an adult
population is about 0.005%/mSv (28). Thus, the American College of
Radiology, through its *Image Gently* program, and other medical
societies, have endorsed the concept of weighing the benefits of the test
with the potential risks from radiation exposure (29). The dose of
combined PET/CT has been studied using a variety of protocols and
systems and ranges anywhere from 3 to 30 mSv per CT scan,
depending on the body part and resolution, with the FDG-PET
contributing approximately 3–4 mSv for a typical administered dose of
12 mCi (28, 30-32). One study evaluating the radiation exposure of
combined PET/CT found that, despite noticeable protocol acquisition
differences, the average effective dose for patients undergoing high-
quality whole-body PET/CT using FDG was approximately 25 mSv
(33).

*FDG-PET Imaging Protocols*

Before recommending a PET/CT to a patient, it is important to
acquire information regarding diabetes and recent infections because
these conditions may alter the uptake of FDG on PET/CT scans and
thus affect the results of the imaging study. Additionally, it is important to inquire about the patients’ physical abilities, such as the ability to lie supine and remain still for approximately 15-30 minutes without coughing.

To improve FDG uptake, patients should consume a high fat and protein diet the day before the imaging study is to be performed to reduce myocardial tissue uptake. Patients should also avoid strenuous exercise and alcohol consumption to reduce skeletal muscle uptake. A 4-6 hour fast prior to the administration of FDG is essential to decrease physiologic glucose levels and to reduce serum insulin levels to near basal levels. Patients requiring intravenous fluids should avoid using dextrose or parenteral feedings. A fasting glucose level greater than 180-200 mg/dL should prompt rescheduling of the exam or injection of short-acting insulin. FDG tumor uptake is reduced in hyperglycemic states and is preferentially driven into skeletal muscles if injected soon after short-acting insulin administration (Figure 22A).
Figure 22: Poor patient preparation can interfere with PET interpretation and results. Examples include exogenous insulin or post-prandial state (A) which may present identically, and bad injection which results in extravasation of contrast at the injection site (B). Extravasation at the injection site may also result in a false positive PET due to the presence of phantom lesions. Venous clots formed at the injection site may travel to the lungs and appear as positive lesions on PET (C) but show no anatomic abnormality on CT (D), Courtesy of Dr J. Wiersig Concord Imaging San Antonio, TX).
Therefore, if insulin is administered, FDG injection should be delayed by 4 hours. Patients on a long-acting insulin pumps supplemented with short-acting insulin should withhold the short-acting insulin 4 hours prior to FDG injection, but are not required to disconnect their insulin pumps. During injection and uptake phase, the patient should remain seated or recumbent to avoid muscular uptake and remain quiet to reduce laryngeal activity.

Typically, a skull base-to-proximal thigh survey is performed to search for abnormal FDG accumulation. While limited area tumor imaging can be considered, “whole-body” tumor imaging has the advantage of staging the entire body and detecting important “incidental” information—both anatomic and functional—which, if discovered, could alter patient management (Figure 23). The patient should be positioned with the arms elevated over the head if possible. Metallic objects should also be removed from the patient whenever possible due to artifacts. Last, the patient should void before imaging to decrease radiation dose to the renal collecting system and bladder.
Figure 23: Whole-body tumor imaging has the advantage of staging the entire body and detecting important incidental information-both anatomic and functional-which, if discovered, could alter patient management. This study demonstrates an incidental hypermetabolic focus on PET (A, B) that by ultrasound proved to be a breast carcinoma (C) during work up of a pulmonary nodule (not shown).
While the timing of the uptake phase is still under scrutiny, most facilities will begin obtaining images no sooner than 60-90 minutes after injection. The use of intravenous or oral contrast for PET/CT is not necessary, especially for SPN evaluation, and can occasionally result in an overestimation of a lesion’s true metabolic potential or obscure identification of important imaging features, such as calcification within a lesion. However, in certain situations the use of contrast may aid in more accurate lesion evaluation, particularly for complex anatomic locations.

Once the subject is placed in the camera gantry, a low-dose CT scan for attenuation correction with the patient undergoing tidal breathing is obtained. Then, the PET emission scan is acquired. Due to rapid computer reconstruction times, the technologist can quickly review the PET/CT scan for image quality and can repeat selected bed positions or the entire PET/CT scan in the case of dual time point imaging (DTPI) (Figure 24). The studies are typically sent to and archived on PET-specific workstations for quantitative analysis and interpretation. When reviewing PET imaging, it is imperative to have a good understanding of the normal distribution of FDG metabolism, normal variations, and artifacts to avoid misinterpretation. Also,
evaluation of images with and without attenuation correction applied should be reviewed to assess the true activity associated with an SPN (Figure 21).
Figure 24: Dual Time point imaging. Coronal PET imaging of a patient with proven carcinoma (arrow in A and B) during early phase imaging (SUV= 6.8) (A) demonstrates an increase in measured SUV (8.5) in the delay phase image (B), while infectious lesions (arrow in C and D), which can present as positive on PET early phase imaging (SUV= 3.4) (C), demonstrates a decrease in SUV (SUV= 2.5) upon repeat delay phase PET (D).
Factors That Affect Image Quality

Additional factors that can affect image quality with PET/CT imaging include FDG extravasation into the soft tissues at the injection site (Figure 22B) and motion artifacts, especially respiratory motion (Figure 25). Respiratory motion during acquisition of the images can lead to significant artifacts resulting in lesion obscuration or inaccurate lesion localization. A protocol encouraging tidal breathing should allow the PET and CT images to match closely. Unlike thoracic CT, inspiration to total lung volume should not be utilized in PET/CT because it results in respiratory motion misregistration.

A newly developing PET technology is the concept of respiratory-gated PET (RGPET). Respiratory gating during PET scanning may provide improved lesion detection, more accurate quantification, and improved image quality. Respiratory gating uses a respiratory motion detector to co-register respiratory motion with PET image acquisition and allows more accurate lesion measurement and count density assessment (34). Respiratory correction methods can be most helpful when assessing SPNs that are close to the diaphragmatic surfaces where motion of the nodule is most pronounced.
Figure 25: Respiratory motion leading to the “banana sign” in the location of the left hemidiaphragm (arrowheads in A) on PET. Such motion artifact can cause a lesion to appear in a false location or disappear completely. Note the lack of a banana sign on the right due to a paralyzed right hemidiaphragm. Images B-E demonstrate how respiratory motion altered the location of a pulmonary nodule (arrow) so that it appeared as a rib lesion on PET. Close inspection of the CT portion (B) of the PET/CT failed to reveal a bone lesion. Biopsy showed NSCLC.
Quantification of FDG Activity: Standard Uptake Value (SUV)

A semi-quantitative estimate of tumor biological activity, known as the *standard uptake value* (SUV), can be derived. The SUV is a commonly accepted measurement of the degree of metabolic activity within tissue. Elevated SUV values indicate robust tracer uptake whereas a low-level indicates little tracer uptake. The activity of the FDG dose, size and location of the lesion, and the injection-to-scan time are all parameters that affect the SUV. As a result, various institutions may use individualized cut-off values specific to their needs. Typically, the SUV value for discriminating between malignant vs. non-malignant lesions is an SUV>2.5, but this cutoff is arbitrary.

Most workstations that display SUVs display values based on the maximum activity in the hottest pixel (SUVmax) or the mean SUV (SUVmean) for a selected a region of interest. The SUVmax is the value that typically is reported to the clinician. Errors in measurement using either SUVmax or SUVmean can arise due to statistical variation in the count activity of an individual pixel, in the case of SUVmax, or partial volume averaging with surrounding normal tissue when using SUVmean. Being consistent in which parameter used in
most important. For qualitative assessment, tracer activity within an SPN is visually compared with background activity in the mediastinum; activity greater than background suggests a metabolically active lesion (Figures 26 and 27), whereas lack of tracer accumulation suggests benign etiology (Figures 28 and 29). Qualitative assessments by experienced observers provide equally accurate results as quantitative assessments using SUV values (35).
Figure 26: True positive: biopsy proven adenocarcinoma. A pulmonary nodule (arrow) is noted in the right upper lobe on CT (A). Notice the increased activity on PET (B) with attenuation correction, fused PET/CT image (C) and without attenuation correction (D). Panel E demonstrates a Maximum Intensity Projection (MIP) image which is a 3-D representation of the PET data that can be viewed in cine mode on dedicated PET workstations.
Figure 27: False negative lung biopsy. Axial thoracic CT (A) shows a small left upper lobe nodule (arrow). Follow up thoracic CT one year later (B) shows nodule growth (arrow). FDG-PET (C) performed shortly after (B) show hypermetabolic activity within the nodule (arrow). Percutaneous biopsy (D) of the nodule (arrow) was performed, showing only inflammation and non-specific fibrosis. Continued surveillance thoracic CT was not performed. Follow up thoracic CT 2 years after the biopsy (E), obtained for hemoptysis, shows clear growth of the nodule (arrow) and development of cavitation. Carcinoma was proved on repeat biopsy.
**Figure 28:** True Negative FDG-PET. SPN on CT (A) with benign features indicative of granuloma. FDG-PET (B-E) does not show a nodule which is confirmed by a lack of activity PET/CT fusion (C).
Figure 29: True Negative FDG-PET: Bacterial pneumonia (*Moraxella catarrhalis*, arrows) demonstrating the advantage of viewing both PETAC and NACPET. There is a lack of activity confirmed by both the non-attenuation corrected (A) and attenuation corrected (B) images.
FDG-PET for SPN Evaluation

A number of studies have examined the utility of FDG-PET for the evaluation of the SPN (2). In a study of 61 patients, FDG-PET was used to differentiate benign from malignant SPNs with a sensitivity of 93% and a specificity of 88% (36). Additionally, positive and negative predictive values for FDG-PET imaging for the detection of malignant SPNs were 95% and 82%, respectively (36). In a similar study evaluating 43 nodules, Hashimoto, et. al., (37) found 100% sensitivity and 63% specificity for the FDG-PET detection of malignancy within an SPN when standard uptake values >2.5 were present. Orlacchio et. al., (38) found a somewhat lower sensitivity, but higher specificity, of 76.9% and 100%, respectively for the FDG-PET detection of malignant SPNs. A meta-analysis evaluating 1474 pulmonary nodules published in 2001 (35) showed a sensitivity of 96.8% and a specificity of 78% for the detection of malignant SPNs, corresponding to positive and negative likelihood ratios of 4.36 and 0.04, respectively. Overall summary estimates of the sensitivity and specificity for malignant SPN detection range from 80-100% and 40-100%, respectively (2). Summary receiver operating characteristic curves suggest the overall sensitivity for the FDG-PET detection of malignancy within an SPN is
at least 87% with a specificity of 83%; these results are superior to thoracic CT (2).

Limitations of FDG PET/CT for SPN Evaluation

As with any test, false positive and false negative results occur with FDG-PET, and false positive results are more common than false negative ones. False positive FDG-PET examinations generally occur as a result of metabolically active infections or inflammatory lesions (Figures 30 and 31), which show FDG accumulation similar to malignancy. Examples of lesions that may produce false positive FDG-PET results include rheumatoid nodules, granulomas, prior trauma sites, and reactive lymph nodes (39).
**Figure 30:** False Positive SPN with a negative biopsy in a patient with proven sarcoidosis. Notice the hilar and mediastinal activity typical for sarcoid (E). The spiculated lesion in the right middle lobe (A) is hypermetabolic (B-E); however, biopsy did not reveal malignancy.
Figure 31: False positive PET can occur in the setting of inflammation or infection. This example is of biopsy proven coccidiomycosis (arrows, A-D) with no evidence of carcinoma.
One proposed method to better differentiate benign inflammatory processes from malignant lesions and to decrease the false positive rate is through dual time point imaging (DTPI). By imaging a lesion at two different time points following a single injection of FDG and measuring the change in SUV between these two time points, one can assess the likelihood of malignancy within the lesion. Studies have shown that the uptake of FDG in tumors continues to increase for several hours after initial injection, whereas prolonged uptake of FDG in inflammatory lesions and normal tissue is less common (40-42). This is likely related to the low phosphatase activity in cancer cells, and the high glucose uptake through glucose transporter proteins (43). Preliminary studies have shown a positive change in SUV between two time points is characteristic of malignant lung lesions (Figure 24). In a study from Matthies, et. al. (41) dual time point scanning using a threshold value of 10% increase between scan 1 and scan 2 reached a sensitivity of 100% with a specificity of 89% for the detection of malignancy. Although promising, DTPI has yet to be validated for routine clinical use.
False negative results with FDG generally occur in the setting of malignancies with relatively little metabolic activity, such as carcinoid tumors, bronchioloalveolar carcinomas (Figure 32), well-differentiated adenocarcinomas of the lung (Figure 33) or malignancies with low viable tumor mass. It has been suggested that FDG-PET produces false negative results in approximately 50% of patients with bronchioloalveolar carcinoma (38) (Figure 32). Additionally, metastasis from certain lesions, such as renal cell carcinoma, testicular cancer, and prostate malignancy, may show little FDG tracer accumulation and may even be undetectable on FDG-PET. Another situation associated with false negative FDG-PET results occurs in patients with hyperglycemia. In such patients, FDG competes with circulating glucose, resulting in relatively diminished FDG accumulation within the malignant lesion. Finally, small nodules may not be accurately assessed using FDG-PET due to the spatial resolution of PET, which is approximately 7 mm for modern scanners (44). In fact, few data are available regarding FDG-PET performance for nodules <1cm (2). In general, negative FDG-PET results for nodules <1 cm, and particularly for nodules <7 mm, do not confidently exclude malignancy (2, 35).
Figure 32: False negative FDG-PET CT: bronchioloalveolar carcinoma. Axial thoracic CT performed in 2006 (A) shows a lobulated right lower lobe pulmonary nodule (arrow) with internal lucencies or air bronchograms. FDG-PET CT (B) performed near the time of (A) shows no significant tracer accumulation within the right lower lobe nodule (arrow); peak SUV was 1.3. Note that the FDG activity within the nodule is not increased compared with mediastinal blood pool. Follow up thoracic CT scan performed in 2007 (C) shows slight change in the appearance of the nodule (arrow), and the nodule measured slightly larger. Repeat FDG-PET CT (D) now shows slightly increased metabolic activity within the lesion (arrow); peak SUV was 2.7. The activity within the nodule (arrow) is very slightly increased compared to mediastinal blood pool activity (peak SUV = 2.6). Resection subsequently proved bronchioloalveolar carcinoma.
**Figure 33**: False negative FDG-PET CT: well-differentiated pulmonary adenocarcinoma. Axial thoracic CT performed in January, 2006 (A) shows a lobulated left upper lobe pulmonary nodule (arrow). FDG-PET CT (B, C) performed shortly after (A) shows no significant tracer accumulation within the left upper lobe nodule (arrows). On the PET image (left panel, B), note that the small area of activity (arrow) is not increased compared to blood pool activity in the mediastinum (far left of the image). The fused PET/CT (C) shows no increased activity within the nodule (arrow). Follow up thoracic CT scans performed in August of 2006 (D) and March of 2007 (E), shows enlargement of the nodule (arrows). Biopsy subsequently proved adenocarcinoma.
In addition to the role of SUV in planning the evaluation of an SPN, SUVs may also allow assessment of the prognosis of patients with nodules subsequently proven to be malignant. Because SUV values allow for quantitative assessment of the metabolic activity within a lesion, they may prove to be a reliable tool for predicting tumor progression, response to therapy, and overall survival in oncology patients. A meta-analysis has shown that patients with malignant lesions showing high SUV values, at all non-small cell lung carcinoma (NSCLCA) stages, have a poorer prognosis than patients with lower SUV values (45) (Figure 34). Similarly, patients with stage I NSCLC who have lower FDG uptake at FDG-PET examinations have an improved prognosis compared with stage I NSCLCA patients with malignancies showing high metabolic activity (46).
**Figure 34:** PET has important implications in predicting prognosis. This patient displays features predictive of inflammatory, aggressive lung cancer. Notice the increased bone marrow uptake (arrowheads, A, B) presumably indicative of high levels of stimulatory cytokines secreted by the carcinoma (arrows, A-C). The higher the SUV the more biologically aggressive the lesion can behave.
*Integrated PET/CT*

Integrated PET/CT scanners fuse images obtained from both PET and CT, allowing for the combined anatomical detail found on thoracic CT with the metabolic localization of PET scans. The combination of anatomical mapping and physiological imaging afforded by integrated PET/CT enhances diagnostic accuracy and provides improved characterization of SPNs as either benign or malignant compared with either modality alone. One study of 42 patients demonstrated that CT and PET alone each correctly characterized 74% of SPNs as benign or malignant, while combined PET/CT characterized 93% of SPNs correctly (Figure 35) (47). PET/CT has mostly replaced dedicated PET in current practice and early systems that used CT for attenuation correction and localization of abnormalities have been replaced by diagnostic-quality CT.
Figure 35: PET with image fusion (PET/CT) allows for the proper identification of metabolically active lesions (arrows, A-C). When multiple lesions are discovered on CT (A), PET/CT may aid in guiding biopsy. The PET positive posterior nodule was carcinoma (arrows) of the lung (true positive) while the anterior nodule (arrowheads, A and C) was a granuloma (true negative).
**PET/CT in Guiding Interventional Procedures**

FDG PET/CT may aid in biopsy and treatment planning. In patients with multiple pulmonary nodules or even those with an SPN, the location that has the greatest FDG metabolic activity should be targeted for percutaneous tissue sampling if possible and those areas of little or no FDG metabolism should be avoided. For patients with indeterminate or non-diagnostic tissue sampling results, FDG PET can serve as a “metabolic biopsy.” For example, Hain, et al., (48) evaluated 63 subjects with FDG PET who had either undergone unsuccessful biopsy or deferred biopsy because it was considered too dangerous. Using a SUV>2.5 cut-off analysis, positive and negative predictive values were 90% and 85%, respectively. These authors concluded that such a high positive predictive value means that a positive scan must undergo further investigation, while lack of FDG uptake allows an indeterminate SPN to be safely followed.

In patients with metabolically active SPNs subsequently proved to be malignant, PET/CT can be used for radiation treatment planning purposes in patients who are not candidates for surgery.
Results and Discussion

**Management Strategies for the SPN**

The primary goals for the management of SPNs are: 1. Early detection of malignancy; 2. Avoidance of unnecessary intervention / surgery for patients with benign nodules, and; 3. Efficient and cost-effective use of resources, including minimizing the use of radiation.

Most SPNs in adult patients discovered at chest radiography, if not shown to be stable for more than 2 years and without benign features, should be evaluated with thoracic CT (44). Thoracic CT is used to characterize the nodule and generate an assessment of the likelihood of malignancy using the morphological features described previously. In some patients, definitively benign nodule features will be evident at CT, with further management conducted accordingly. In other patients, the nodule will remain indeterminate following thoracic CT, and further evaluation will be required. In such patients, methods that may be employed include FDG-PET, thoracic CT or MR using a contrast enhancement protocol, serial CT surveillance to assess for growth over time, biopsy, or resection.

For indeterminate nodules >1 cm, FDG-PET is probably the most useful choice for further assessment because FDG-PET provides nearly
equivalent sensitivity to nodule enhancement using CT for malignancy detection, but with superior specificity. Furthermore, FDG-PET provides additional prognostic information for patients subsequently proved to have malignancy. Finally, FDG-PET may occasionally disclose other unsuspected sites of disease that may suggest a diagnosis or allow for less invasive intervention than lung biopsy. Negative PET results provide strong, but not definitive, evidence that an SPN is benign. Typically in the setting of negative FDG-PET results, serial thoracic CT is advisable to assess for growth- this approach allows for detection of slow growing malignancies of low metabolic activity (Figures 32 and 33).

For nodules <1 cm, serial thoracic CT is probably the most efficacious approach for assessing the malignant potential of a nodule. The interval at which CT should be performed depends on the size of the nodule and the presence or absence of historical factors known to influence the likelihood of malignancy within a pulmonary nodule. A number of approaches to serial surveillance of small nodules have been advocated in the literature, largely in the context of lung cancer screening studies. The approach chosen should be tailored to the patient and the characteristics of the practice location. The Fleischner
Society (1) has published recommendations for subcentimeter nodule surveillance using thoracic CT (Table 3). These recommendations provide an evidence-based approach to small nodule management and may be modified to suit the needs of a particular practice.
### Table 3: Fleischner Society recommendations for follow-up and management of nodules <8 mm detected incidentally at non-screening thoracic CT (1)

<table>
<thead>
<tr>
<th>Nodule Size*</th>
<th>Low-Risk Patient†</th>
<th>High-Risk Patient**</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 mm</td>
<td>No follow-up needed†</td>
<td>Follow-up CT at 12 mo; if unchanged, no further follow-up‡</td>
</tr>
<tr>
<td>&gt;4, &lt;6 mm</td>
<td>Follow-up CT at 12 mo; if unchanged, no further follow-up‡</td>
<td>Initial follow-up CT at 6-12 mo then 18-24 mo if no change</td>
</tr>
<tr>
<td>&gt;6, &lt;8mm</td>
<td>Initial follow-up CT at 6-12 mo then at 18-24 mo if no change</td>
<td>Initial follow-up CT at 3-6 mo, then at 9-12 mo and 24 mo if no change</td>
</tr>
<tr>
<td>&gt;8</td>
<td>Follow-up CT around 3, 9, 24 mo. Dynamic contrast-enhanced CT, PET, and/or biopsy</td>
<td>Same as for low-risk patient</td>
</tr>
</tbody>
</table>

**Notes:**
- Newly detected indeterminate nodules in patients 35 years or older
- *Average length and width
- †Minimal or absent history of smoking or other known risk factors
- **History of smoking or other known risk factors
- ‡The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker
- §Non-solid (ground-glass) or partly solid nodules may require longer term follow up to exclude indolent adenocarcinoma
In the setting of known malignancy, the presence of small nodules constitutes a dilemma. Unlike patients enrolled in lung cancer screening studies, in which the likelihood of malignancy within a small nodule discovered at thoracic CT is ≤1%, small nodules in oncology patients may frequently harbor malignancy (13). In such patients, frequently short interval surveillance CT is used to assess for growth, but the frequency at which thoracic CT should be performed is unclear. Recently, Munden, et. al. (49) showed that 28% of small nodules detected at thoracic CT performed on oncology patients will show growth, suggesting metastatic disease; such growth is usually demonstrable early- at 3 – 6 months. These investigators also found that small nodules stable in size for one year are unlikely to represent metastases (49).

As discussed previously, nodules detected at thoracic CT shown to be stable in size or volume for 2 years may be considered benign, with the caveats discussed previously. Ground-glass opacity nodules (part-solid or subsolid nodules) should be followed for a more extended period of time before being dismissed as benign- 5 years has been suggested as the appropriate duration of follow up for such nodules (2, 14).
When a nodule undergoing surveillance CT shows growth, or a lesion undergoing FDG-PET shows elevated metabolic activity, absent a clinical correlate (such as recent infection or non-infectious inflammatory conditions known to produce nodular lung disease), a tissue diagnosis is usually warranted. Percutaneous biopsy can be useful in such circumstances. Wallace, et. al., (50) showed that the diagnostic accuracy for percutaneous biopsy of nodules 8-10 mm is nearly as high as that for larger lesions (50), although the diagnostic yield falls for nodules ≤7 mm. When non-diagnostic results occur with percutaneous lung biopsy, the nodule should undergo repeat transthoracic biopsy, thoracoscopic biopsy, or serial thoracic CT for growth assessment (Figure 27) to completely exclude malignancy.

Thoracoscopic biopsy is another option for establishing the diagnosis for small pulmonary nodules. Localization techniques, such as use of hook wires, dye injection, or radionuclide injection, to assist the intraoperative localization of small nodules may be performed.

Finally, for operable patients with SPNs who are at high risk for malignancy, surgery is an appropriate diagnostic and potentially therapeutic option. In such patients, even negative non-invasive evaluations, such as negative FDG-PET and CT nodule enhancement
studies, cannot lower the probability of malignancy to a low enough level to allow an observational strategy (44). Similarly, transthoracic biopsy is not recommended in such patients because positive results will not change management and negative results are insufficiently reliable to exclude malignancy (44). Nevertheless, in practice, FDG-PET and a pre-operative tissue diagnosis are often obtained in such patients, often to justify to the patient the risks of and need for surgical treatment of an SPN.
Future Directions

The role of imaging modalities including PET/CT in the diagnosis of the SPN is constantly expanding. It is important to continue to evaluate current practices of management in order to characterize SPNs and evaluate patients for risk of malignancy.
Conclusions

The differential diagnosis of an SPN is broad and management depends on whether the lesion is benign or malignant. The probability of malignancy in an indeterminate SPN discovered at chest radiography in an adult patient is approximately 40%. The goal of imaging studies and minimally invasive procedures is to modify this probability to a high enough level to warrant surgery or to a low enough level to allow observation of the nodule.

Physicians are commonly challenged to balance the benefits of early diagnosis with the potential risks and costs of unnecessary intervention. The optimal balance of diagnostic testing and intervention depends on a number of factors, and no single approach is appropriate for every patient. A number of evidence-based approaches to the evaluation of the SPN have been published, and adoption of one of these approaches, with modification to suit the needs of the particular practice, allows for early diagnosis of malignancy while minimizing the risk for unnecessary intervention or needless surgery.
References


16. Berger WG, Erly WK, Krupinski EA, Standen JR, Stern RG. The solitary pulmonary nodule on chest radiography: can we really tell if the nodule is calcified? AJR Am J Roentgenol 2001; 176:201-204.


