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February 2021 Imaging Case of the Month: An Indeterminate Solitary Nodule

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Clinical History: A 43 -year-old woman with no past medical history presented to the Emergency Room with complaints of right chest wall pain extending into the right upper quadrant. The patient was a non-smoker, denied any allergies, and was not taking any prescription medications.

Key Words: solitary pulmonary nodule, chest x-ray, CT scan, diagnosis, transcutaneous needle biopsy, Pulmonary epithelioid hemangioendothelioma, pleural metastasis, pleural effusion, 18FDG-PET scan, calcification,

Physical examination showed the patient to be afebrile with normal heart and respiratory rates and blood pressure = 110/75 mmHg. Her room air oxygen saturation was 99%.

The patient's complete blood count and serum chemistries showed normal values. Her liver function testing and renal function testing parameters were also within normal limits.

Which of the following represents an appropriate next step for the patient's management?

1. Perform abdominal ultrasound
2. Perform chest radiography
3. Perform unenhanced chest CT
4. More than one of the above
5. None of the above

Correct!

4. More than one of the above

Both chest radiography and abdominal ultrasound are reasonable initial tests to perform when a patient in the Emergency Room presents with chest and abdominal pain. Chest CT is probably premature at this point, and may be reserved for more specific clinical indications or for further evaluation when initial chest radiography is abnormal and the clinical presentation remains unclear.

The patient underwent right upper quadrant ultrasound (images not shown) that was interpreted as unremarkable; no gallbladder wall thickening or biliary duct dilation was noted and no gallstones were seen. The patient then underwent nuclear medicine biliary scintigraphy with hepatobiliary iminodiacetic acid (“HIDA” scan; images not shown) which showed “sluggish” tracer uptake by the gallbladder, interpreted as potentially representing cholecystitis.

Which of the following represents an appropriate next step for the patient’s management?

1. Endoscopic retrograde cholepancreatography (ERCP)
2. Laparoscopic cholecystectomy
3. Open cholecystectomy
4. Perform ¹⁸F-DG-PET scan
5. Perform MRI cholepancreatography

Correct!

5. Perform MRI cholepancreatography

Among the choices listed, MR cholepancreatography (MRCP) is the most reasonable answer. Surgical removal of the gallbladder, either by laparoscopic or open cholecystectomy, is premature at this point. Although the patient does have right upper quadrant pain, there are numerous causes of such pain and thus far there are few data implicating the biliary system as the cause of her pain- her liver and biliary enzymes were normal and her right upper quadrant ultrasound examination was unremarkable. The “sluggish” appearance of tracer in the gallbladder at nuclear medicine scintigraphy (HIDA scan) is very non-specific. The absence of tracer accumulation within the gallbladder is taken as evidence of acute cholecystitis, but this was not the test result. Rather, the “delayed” appearance of tracer in the gallbladder can be associated with chronic cholecystitis, as can “reduced gallbladder ejection fraction,” but these findings are non-specific. Commonly, chronic cholecystitis is associated with gallstones, which were not seen in this patient, so the equivocal findings at nuclear medicine scintigraphy should be regarded with suspicion. For this reason, before any invasive intervention is planned, further data supporting a biliary cause for the patient’s presentation is needed, and MR cholepancreatography could be helpful in this regard. ¹⁸F-DG-PET scan does not play a role in the evaluation of patients with acute presentations in the Emergency Room.

The patient underwent laparoscopic cholecystectomy. Her patient persisted post-operatively and she re-presented to her physician in an outpatient setting with the same complaints of right chest and upper quadrant pain. See underwent frontal chest radiography (Figure 1).

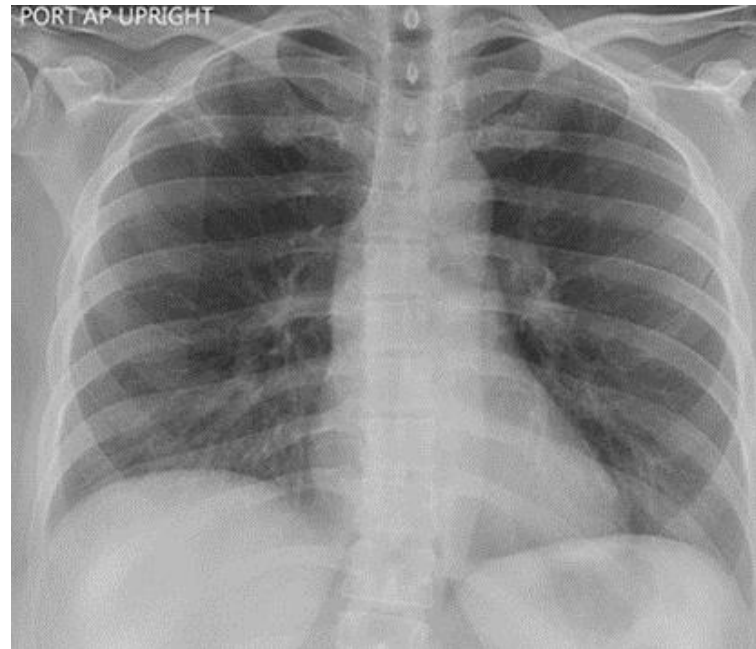


Figure 1. Initial frontal chest radiography. Which of the following represents an appropriate interpretation of her frontal chest radiograph?

1. The frontal chest radiograph shows a vague right apical nodule
2. The frontal chest radiography shows a right pleural effusion
3. The frontal chest radiography shows cardiomegaly
4. The frontal chest radiography shows multifocal consolidation
5. The frontal chest radiography shows peribronchial and mediastinal lymphadenopathy

Correct! 1.

The frontal chest radiograph shows a vague right apical nodule

The frontal chest radiograph (Figure 1) shows a vague, poorly visualized right apical nodule (Figure 2).

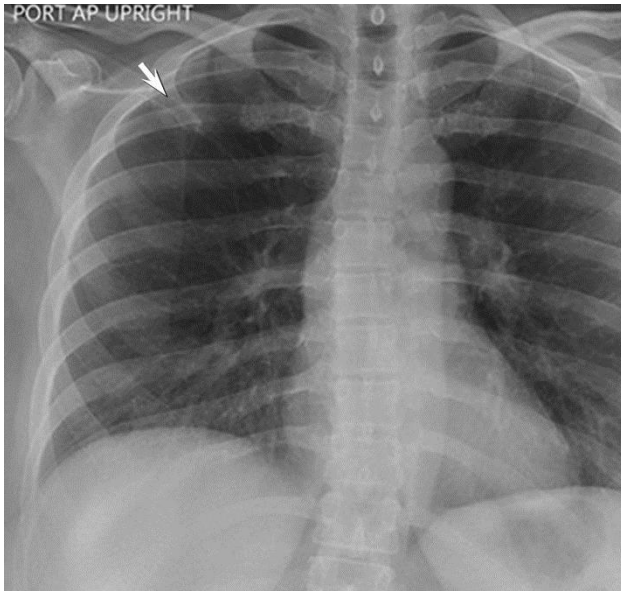


Figure 2. Initial frontal chest radiograph (same as Figure 1) but with an arrow showing a poorly defined nodular opacity in the right apex.

The heart size is normal, the lungs appear clear otherwise, the mediastinal and hilar contours appear normal, and no pleural effusion is seen.

Which of the following represents an ***appropriate differential diagnostic consideration*** for the patient's chest radiographic findings?

1. Bronchogenic malignancy
2. Coccidioidomycosis
3. Hamartoma
4. Inflammatory myofibroblastic tumor
5. All of the above

Correct!
5. All of the above

All of the listed entities, and many more, may present as a solitary pulmonary nodule at chest radiography.

Which of the following represents *an appropriate next step* for the patient's management?

1. ¹⁸F-FDG-PET scan
2. Chest MRI
3. Comparison to prior chest radiography
4. Lateral decubitus chest radiography
5. More than one of the above

Correct!

3. Comparison to prior chest radiography

Whenever a lesion is discovered at chest imaging, comparison to older chest imaging studies is of paramount importance. If a chest lesion can be shown to be stable for a significant length of time, the evaluation of a chest lesion may be tempered, saving expense, potential radiation exposure, patient anxiety, and possibly even complications. For this patient, if the right upper lobe lesion were shown to be unchanged for several years, rather than pursuing a potential malignancy evaluation, the lesion may be followed with imaging. Chest MRI plays little role in the evolution of a solitary pulmonary nodule. While pulmonary opacities can be visualized at chest MRI, and MRI has the advantage of the lack of ionizing radiation, evaluation of the pulmonary parenchyma is generally more rewarding using CT. Lateral decubitus chest radiography is potentially useful for evaluating pleural effusions (typically to determine if pleural fluid is mobile or flowing, or for the detection of pneumothorax), but does not play a role for the evaluation of a solitary pulmonary nodule. ¹⁸F-DG-PET scan may be an appropriate test for this patient, but is generally performed in patients with solitary pulmonary nodules following chest CT showing indeterminate findings.

The patient had never undergone previous chest imaging. Coccidioidomycosis and Quantiferon testing were negative.

Which of the following represents an appropriate next step for the patient's management?

3. Perform follow up chest radiography in 3 months
4. Perform unenhanced chest CT
5. Perform ¹⁸F-DG-PET scan

1. Perform ¹⁸F-DG-fibroblastic activation protein inhibitor (FAPI) scan
2. Perform ¹⁸F-DG-prostatespecific membrane antigen (PMSA) scan

Correct!

4. Perform unenhanced chest CT

Unenhanced chest CT is typically the next test performed when an indeterminate solitary pulmonary nodule is encountered at chest radiography. As noted above, ^{18}F FDG-PET scan may be an appropriate test for this patient, but is generally performed in patients with solitary pulmonary nodules following chest CT showing indeterminate findings. Follow up chest radiography to assess for stability may be an appropriate approach when a lesion is considered low risk for malignancy. This patient's relatively young age (43-years-old) may favor a benign etiology, but the size (2 cm), ill-defined nature of the lesion, and the lack of clear visualization of calcification within the nodule render the lesion indeterminate in nature, and no clinical or laboratory tests suggest that an infectious granuloma may be cause of this lesion. ^{18}F FDG-fibroblastic activation protein inhibitor (FAPI) scanning utilizes peptidomimetic quinolone derivatives that bind to fibroblastic activation protein expressed on cancer-associated fibroblasts in tumor stroma, whereas ^{18}F FDG-PET exposes malignancy through detection of glycolytic activity in neoplasms. Initial testing has shown that ^{18}F FDG-FAPI may accurately detect a number of different malignancies, but is not in widespread use for the evaluation of an indeterminate solitary pulmonary nodule. ^{18}F FDG-prostatespecific membrane antigen [PMSA] has been utilized for the detection of prostate carcinoma, which is not a consideration for this patient.

The patient underwent enhanced chest CT (Figure 3).

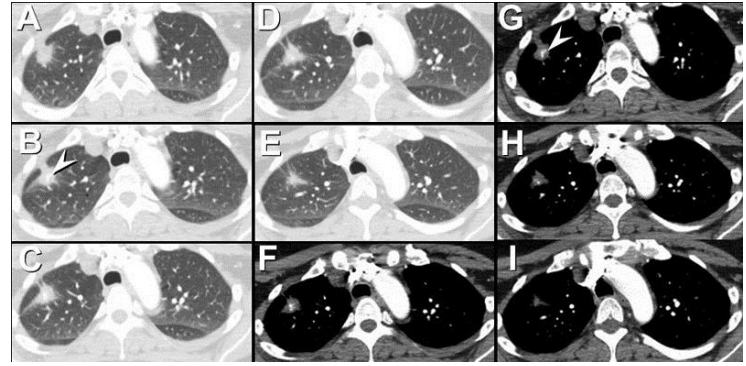


Figure 3. Axial enhanced chest CT displayed in lung (A-E) and soft tissue (F-I) windows shows a spiculated apical nodule with a pleural tail. The lesion contains a small focus of calcium (arrowheads).

Which of the following statements regarding the chest CT is most accurate?

1. The chest CT shows a benign lesion in the right upper lobe
2. The chest CT shows a malignant lesion in the right upper lobe
3. The chest CT shows an indeterminate lesion in the right upper lobe
4. The chest CT shows numerous small pulmonary nodules in addition to the right upper lobe nodule
5. The chest CT shows peribronchial and mediastinal lymphadenopathy

Correct!

3. The chest CT shows an indeterminate lesion in the right upper lobe

The enhanced chest CT shows a spiculated lesion with a pleural tail in the right apex. While the lesion shows some features associated with pulmonary malignancy- soft tissue, spiculation, and a pleural tail- the lesion also shows at least one feature suggesting a benign etiology- the presence of calcium. Note, however, while *the presence of calcification* within a pulmonary nodule is far more commonly associated with a benign etiology than a malignant one, *the pattern* of calcification (Figure 4), not the mere presence or absence of calcium, within a nodule, is a feature that has been regarded as an *absolute indicator* of a benign cause for a nodule at chest radiography (the other being clear evidence of nodule stability for more than 2 years).

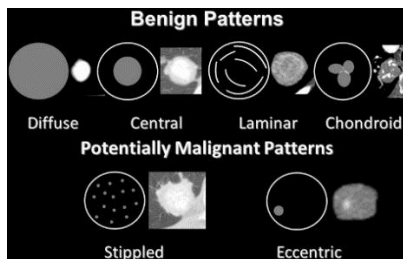


Figure 4. Patterns of nodule calcification-illustrations and CT examples: Benign patterns of calcification within a solitary pulmonary nodule include diffuse, or homogenous, nodule calcification, central (“bull’s-eye”), laminar, or “target” calcification (presenting as concentric rings of calcification), and chondroid, or “popcorn,” calcification. When calcification is found within a pulmonary malignancy, it usually manifests in either a stippled or eccentric pattern; the latter is thought to result from a pulmonary malignancy engulfing a granuloma.

In this case, the patient’s nodule does contain calcium, which portends that the lesion is more likely benign than malignant (as does her relatively young age and lack of smoking history), but this observation alone is not an absolute indicator of benignity because some malignancies, such as neuroendocrine tumors, mucinous carcinomas, and cartilage or bone-forming metastatic lesions, may contain calcium or bone. Furthermore, while the nodule does contain central calcification, there is a substantial amount of non-calcified soft tissue, which renders the lesion radiologically indeterminate. The chest CT shows neither peribronchial nor mediastinal lymph node enlargement, and the lungs appear clear otherwise.

Which of the following represents an appropriate next step for the patient’s management?

1. ^{18}F FDG-PET scan
2. Percutaneous transthoracic needle biopsy
3. Short term follow up chest CT
4. Surgical lung biopsy
5. More than one of the above

Correct!

5. More than one of the above

The right apical nodule in this patient shows features consistent with either benign or malignant etiologies and is therefore the nodule is truly indeterminate. Features favoring a benign etiology for this lesion include the patient's relatively young age, her lack of a history of malignancy, her lack of a smoking history, and the presence of calcium within the lesion. Features suggesting the possibility of malignancy for this nodule include the presence of a significant component of non-calcified soft tissue in the lesion, the upper lobe location, the presence of spiculation, and the presence of a pleural tail [this latter feature is relatively minor and equivocal]. A number of on-line calculators can be used to assess the likelihood of malignancy when nodules such as this one are encountered. For example, the Mayo Clinic Malignancy Risk Prediction Model (<https://www.mdcalc.com/solitary-pulmonary-nodule-spn-malignancy-risk-score-mayo-clinic-model>) estimates the probability of malignancy for this 2 cm nodule to be 31.8%, whereas the Brock University calculator (<https://www.uptodate.com/contents/calculator-solitary-pulmonary-nodule-malignancy-risk-in-adults-brock-university-cancer-prediction-equation>) suggests a likelihood of malignancy of 41.4% for this nodule. The Mayo Clinic Malignancy Risk Prediction Model indicates that serial evaluation for stability is appropriate for nodules with <2% probability of malignancy, percutaneous tissue sampling with "lower" probabilities for malignancy (2-20%), and surgery when the probability of malignancy within a solitary pulmonary nodule exceeds 70%. Therefore, serial evaluation of this nodule to detect growth is not an optimal choice. Both percutaneous transthoracic lung biopsy and ¹⁸F-DG-PET scan are reasonable choices for further evaluation of this patient's nodule. While surgical lung biopsy could be considered by

some to be needlessly invasive for the evaluation of this nodule, it could also be argued that there are enough features that predict that this nodule is malignant that the lack of malignant features at percutaneous transthoracic needle biopsy may not reliably exclude malignancy, and therefore complete surgical excisional biopsy is required to definitively exclude a cancerous etiology for this nodule.

The patient underwent ¹⁸F-DG-PET scan (Figure 5).

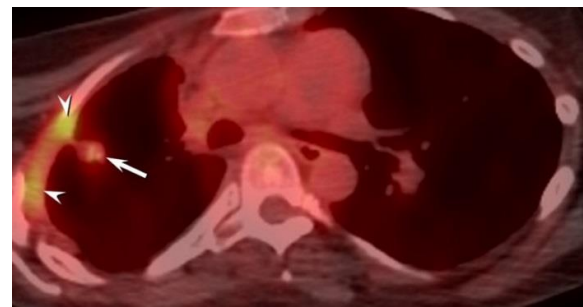


Figure 5. Axial ¹⁸F-DG-PET scan shows mildly increased tracer accumulation within the peripheral right upper lobe partially calcified pulmonary nodule (arrow). Elevated tracer utilization within the immediately adjacent pleura (arrowheads) is also noted. Which of the following statements regarding the chest CT is most accurate?

1. The ¹⁸F-DG-PET scan is technically limited and therefore not interpretable
2. The ¹⁸F-DG-PET scan shows ipsilateral mediastinal lymphadenopathy at the level of the nodule
3. The ¹⁸F-DG-PET scan shows no tracer utilization in the right apical pulmonary nodule
4. The ¹⁸F-DG-PET scan shows only mild tracer utilization in the right apical pulmonary nodule

5. The ¹⁸F-FDG-PET scan shows intense tracer utilization in the right apical pulmonary nodule

Correct!

4. The ¹⁸FDG-PET scan shows only mild tracer utilization in the right apical pulmonary nodule

The ¹⁸FDG-PET scan shows only mild focal tracer accumulation in the right upper lobe nodule, but some moderate tracer activity is also noted in the immediately adjacent pleura. The standard uptake value in the nodule itself was 2.3, with the immediate adjacent pleural activity reaching a standard uptake value of 3.2. No other sites of tracer accumulation were noted on the study, and the study was technically adequate. When incorporating the presence of only faint FDG uptake within the nodule, the Mayo Clinic Malignancy Risk Prediction Model (<https://www.mdcalc.com/solitary-pulmonary-nodule-spn-malignancy-risk-score-mayo-clinic-model>) estimates the probability of malignancy in this nodule to have decreased somewhat to 22.2%.

Several weeks later, the patient continued to complain of worsening chest and right upper quadrant pain which was now complicated by shortness of breath. Repeat frontal chest radiography (Figure 6) was performed.

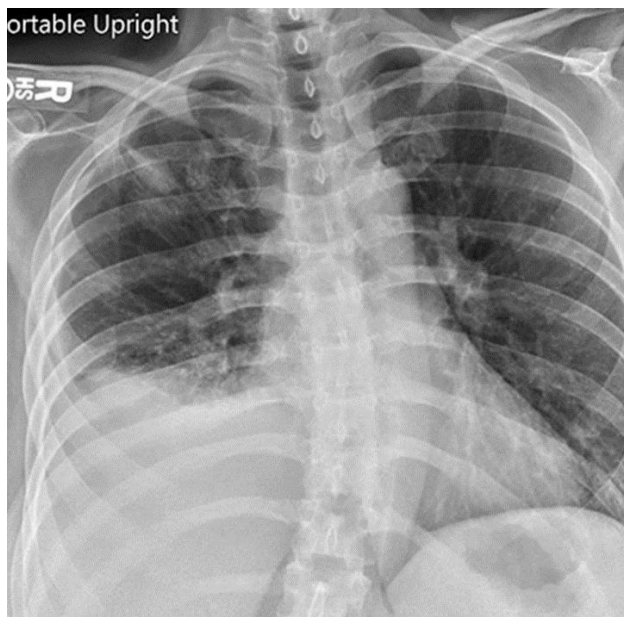


Figure 6. Frontal chest radiography obtained several weeks after the ¹⁸FDG-PET scan.

Which of the following statements regarding the chest radiograph is ***most accurate***?

1. The frontal chest radiograph shows new widespread nodularity
2. The frontal chest radiography shows a new moderate-sized right pleural effusion
3. The frontal chest radiography shows new cardiomegaly suggesting pericardial effusion
4. The frontal chest radiography shows new multifocal consolidation
5. The frontal chest radiography shows new peribronchial and mediastinal lymphadenopathy

Correct!

2. The frontal chest radiography shows a new moderate-sized right pleural effusion

The frontal chest radiograph shows a new moderate-sized right pleural effusion, but there is no evidence of widespread pulmonary nodularity, consolidation, or clear evidence to suggest new peribronchial or mediastinal lymph node enlargement. The heart size remains normal.

Which of the following represents **an inappropriate next** step for the patient's management?

1. MRI of the brain
2. Percutaneous transthoracic needle biopsy
3. Ultrasound-guided right-sided thoracentesis
4. Video-assisted thoracoscopic surgical lung biopsy
5. More than one of the above

Correct!
1. MRI of the brain

Image-guided drainage of the new right pleural effusion is clearly indicated. The development of a new pleural effusion in the context of an unexplained ipsilateral pulmonary nodule, particularly given the tracer accumulation in the pleura at the ¹⁸F-DG-PET scan (Figure 5), is a potentially worrisome situation, and therefore tissue sampling of the right lung nodule is advisable. As noted previously, tissue sampling by percutaneous transthoracic needle biopsy or surgical biopsy is appropriate; however, there is no indication for brain MRI.

The patient underwent percutaneous transthoracic needle biopsy (Figure 7), which only yielded scant blood, inflammatory cells, fibrotic material, and non-specific findings.

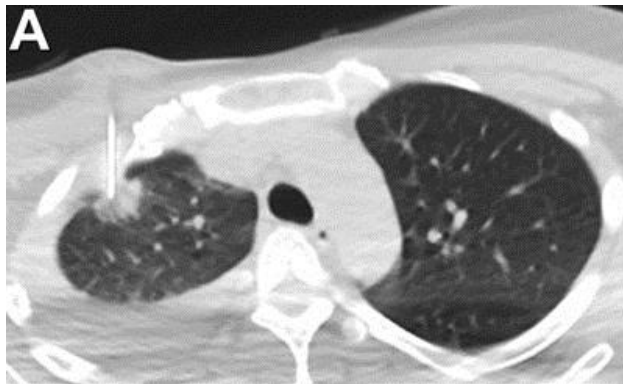


Figure 7. Image acquired during percutaneous transthoracic needle biopsy (A). The right pleural effusion is evident. Imaging immediately following the biopsy procedure shows a right pneumothorax (*, B).

Which of the following represents the ***most appropriate recommendation*** for the patient's management?

1. Bronchoscopy with transbronchial biopsy

2. Cryobiopsy
3. Intercostal arteriography
4. Repeat percutaneous transthoracic needle biopsy
5. Video-assisted thoracoscopic surgical lung biopsy

Correct!

5. Video-assisted thoracoscopic surgical lung biopsy

Repeating the percutaneous transthoracic needle biopsy is not “wrong,” but the imaging during this procedure (Figure 7) shows that the needle was appropriately placed, yet the results were nondiagnostic, suggesting a low likelihood that a repeat procedure would be successful. For this reason, a definitive procedure- video-assisted surgical lung biopsy- is indicated. The peripheral location of the nodule makes it relatively unsuitable for bronchoscopic evaluation. Cryobiopsy is generally reserved for patients with diffuse lung diseases, not solitary pulmonary nodule tissue sampling. Intercostal arteriography is typically employed to control bleeding, commonly for patients with traumatic chest wall injury or hemothorax, and neither are considerations for this patient.

The patient underwent right-sided video-assisted thoracoscopic surgical lung biopsy. During the procedure the surgeon could visualize right-sided pleural nodularity and sampling of the right-sided pleura in the upper, anterior middle, and right lower chest was conducted, and the nodule was resected. Histopathological analysis of the nodule and all of the sampled pleura showed epithelioid hemangioendothelioma.

The patient was treated with several cycles of paclitaxel/gemcitabine as well as pazopanib following right pleurectomy, decortication, diaphragmatic resection and reconstruction, with liver resection also given that disease extended across the diaphragm from the right-sided pleura into the liver. Despite this therapy, her disease subsequently progressed and she died about 2 years after her right upper lobe lesion was discovered.

Diagnosis: Pulmonary epithelioid hemangioendothelioma with pleural metastatic disease

References

1. Calais J, Mona CE. Will FAPI PET/CT Replace FDG PET/CT in the Next Decade? Point-An Important Diagnostic, Phenotypic, and Biomarker Role. *AJR Am J Roentgenol.* 2021 Feb;216(2):305-306. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Truong MT, Ko JP, Rossi SE, Rossi I, Viswanathan C, Bruzzi JF, Marom EM, Erasmus JJ. Update in the evaluation of the solitary pulmonary nodule. *Radiographics.* 2014 Oct;34(6):1658-79. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Erasmus JJ, McAdams HP, Connolly JE. Solitary pulmonary nodules: Part I. Evaluation of the indeterminate nodule. *Radiographics* 2000; 20(1):43-58. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Erasmus JJ, McAdams HP, Connolly JE. Solitary pulmonary nodules: Part II. Evaluation of the indeterminate nodule. *Radiographics* 2000; 20(1):59-66. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Patel VK, Naik SK, Naidich DP, Travis WD, Weingarten JA, Lazzaro R, Gutterman DD, Wentowski C, Grosu HB, Raouf S. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 1: radiologic characteristics and imaging modalities. *Chest* 2013; 143(3):825-839. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Patel VK, Naik SK, Naidich DP, Travis WD, Weingarten JA, Lazzaro R, Gutterman DD, Wentowski C, Grosu

- HB, Raouf S. A practical algorithmic approach to the diagnosis and management of solitary pulmonary nodules: part 2: pretest probability and algorithm. *Chest* 2013; 143(3):840-846. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Gould MK, Donington , Lynch WR, Mazzone PJ, Midhun DE, Naidich DP, Soylemez Wiener R. Evaluation of individuals with pulmonary nodules: when is it lung cancer? *Diagnosis and management of lung cancer, 3rd, ed:* American College of Chest Physicians evidence based clinical practice guideline. *Chest* 2013; 143(5)(Suppl):e93S-120S. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. *Arch Intern Med* 1997; 157(8):849-855. [\[CrossRef\]](#) [\[PubMed\]](#)