

# Thoracic Oncology Cases



**Thailand**  
Bangkok | 10-12 April



# Case 1



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- A 68-year-old active smoker is seen in your outpatient clinic for follow-up of known emphysema. He reports that his health is at his baseline. He can walk a mile if he paces himself. He has a chronic non-productive cough, unchanged over the past year. He had one acute exacerbation of his emphysema requiring outpatient treatment 6 months ago. He failed an attempt at smoking cessation and has now accumulated 55 pack-years of smoking. After a discussion about the benefit and harms of lung cancer screening you arrange for him to visit your lung cancer screening program.
- The presence of emphysema is associated with a lower:
  - A. proportion of screen detected cancers that are adenocarcinoma.
  - B. risk of a complication from lung nodule biopsy.
  - C. risk of having lung cancer.
  - D. likelihood of finding a lung nodule on the screening CT.

## Discussion

- Cohorts with emphysema have a **higher proportion of screen and non-screen detected squamous cell cancers** than those without emphysema (choice A is correct).
- In the US, lung cancer screening with a low radiation dose chest CT scan is currently recommended annually for individuals deemed to be at high risk for developing lung cancer based on their **age (55-77 years) and smoking history (at least 30 pack-years, smoked in the past 15 years)**.
- This recommendation is based on an interpretation that the **benefit** of 16-20% relative reduction in lung cancer deaths found in the National Lung Screening Trial **outweighs the screen related harms** (e.g. imaging and invasive evaluation of lung nodules, overdiagnosis/treatment, radiation exposure).

## Discussion

- If everyone eligible for lung cancer screening is screened, it is estimated that **35-40% of all lung cancers** would be screen detected.
- To increase the portion of lung cancers that are screen detected, and minimize screening harms to those unlikely to develop lung cancer, some have proposed the use of **lung cancer risk calculators** to select individuals for screening.
  - A few risk calculators have been shown to be **slightly more accurate** than current eligibility criteria.
  - Risk calculators have not been evaluated in a **clinical utility** study.
  - Risk factors that are included in the calculators could shift the **patient and cancer phenotype** in a manner that impacts the balance of benefit to harm. COPD and/or emphysema is included in some of the models.

## Discussion

- It is well established that those with emphysema have:
  - a **higher risk of developing lung cancer** (choice C is incorrect),
  - **more lung nodules** on the screening CT (choice D is incorrect),
  - a greater **risk of complications** from lung nodule biopsies (choice B is incorrect),
  - a greater **risk of complications** from lung resection, and
  - a **poorer survival** after surgery for stage I lung cancers.
- In subgroup analysis there was **no reduction in squamous cell lung cancer mortality in the NLST**, a histology seen more often in those with than those without emphysema.

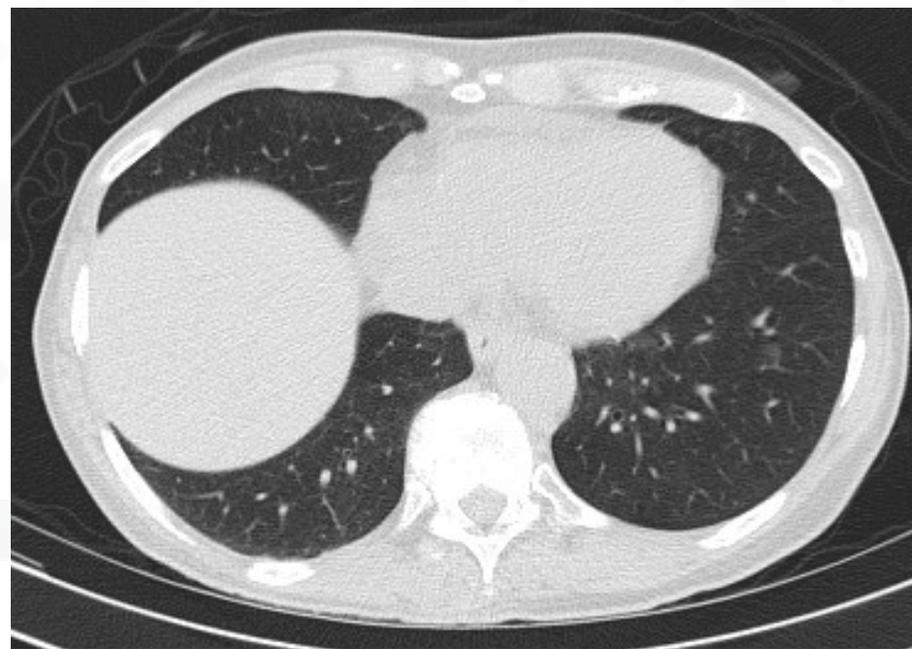
# Case 2



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A 64 year old never smoker presents for evaluation of lung nodules discovered on imaging performed for evaluation of abdominal pain. She is active without limiting dyspnea. She does not have new respiratory or systemic symptoms. Her other history includes monoclonal gammopathy of undetermined significance, latent TB post isoniazid treatment, hypothyroidism, and migraines. Her chest CT shows a 6 mm solid non-calcified nodule in the right middle lobe and a 6 mm pure ground glass nodule in the left lower lobe. There is no adenopathy or pleural disease.



## Question

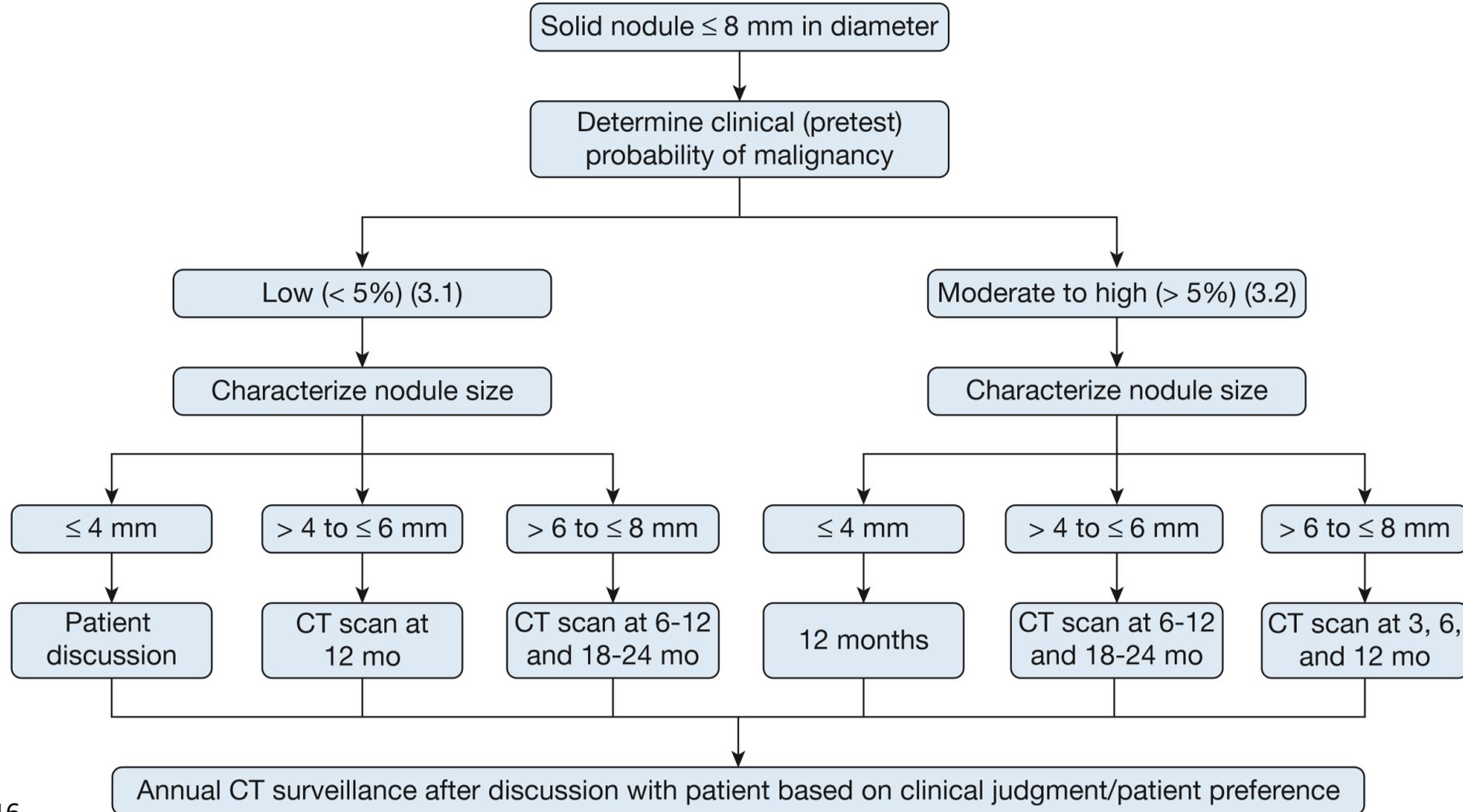
Which of the following statements about management of her lung nodules is correct?

- A. Recommendations for the next surveillance CT scan are the same for both nodules. Recommendations for additional surveillance CT scans (after the next one) are at the same interval for both nodules.
- B. Recommendations for the next surveillance CT scan are the same for both nodules. Recommendations for additional surveillance CT scans (after the next one) are at different intervals for each nodule.
- C. Recommendations for the next surveillance CT scan are different for each nodule. Recommendations for additional surveillance CT scans (after the next one) are at the same interval for both nodules.
- D. Recommendations for the next surveillance CT scan are different for each nodule. Recommendations for additional surveillance CT scans (after the next one) are at different intervals for each nodule.

## Discussion

- Lung nodules are commonly identified on chest CT imaging. The **majority of the nodules are small and solid, with a very low risk of being malignant.**
- **Solid nodules and sub-solid nodules** (pure ground glass and part-solid nodules) have different rates of malignancy and different growth rates when malignant, thus the management **recommendations for these two categories of lung nodules differ.**
- Recommendations for evaluation of a **6 mm solid nodule and a 6 mm pure ground glass nodule** include the **same initial surveillance interval (6-12 months) but different additional surveillance intervals (12 months later for the solid nodule and 2 years later for the ground glass nodule)** (choice B is correct; choices A, C, and D are incorrect).

# Discussion



# Case 3



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A 57 year old male active smoker presents with an incidentally discovered solid lung nodule. A chest CT scan, performed after a motor vehicle accident, revealed a spiculated 15 x 11 mm solid non-calcified nodule in the left upper lobe. He is without cardiopulmonary or systemic symptoms. He is an active smoker of 1 pack per day for the past 40 years. He lives in a region that is endemic for Histoplasmosis. His other medical history includes emphysema. His mother had lung cancer. You estimate the probability that the lung nodule is malignant to be 48% based on the Mayo lung nodule risk calculator.



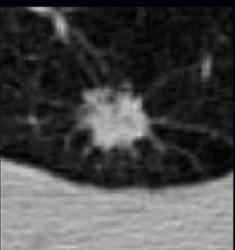
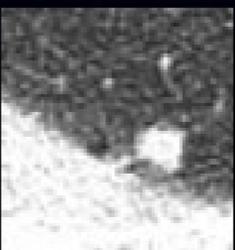
## Question

Which of the following statements is true?

- A. A negative FDG-PET scan result has a high enough negative predictive value to recommend surveillance of the nodule with serial CT imaging.
- B. The calculated probability of malignancy varies 2-fold depending on which risk calculator is used.
- C. The yield of navigational bronchoscopy is expected to be  $> 80\%$ .
- D. A course of antibiotics should be administered before evaluating the nodule further.

# Discussion

- Solid lung nodules larger than 8 mm in diameter are evaluated by first **estimating the probability that the nodule is malignant**.
  - Lung nodule risk calculators include variables that are known to be independently associated with the etiology of lung nodules.
  - Some have been developed in populations with a **low prevalence** of malignancy (e.g. Brock model, screening population), while others have been developed in populations with **moderate** (e.g. Mayo model, 24% prevalence) and **high prevalence** (e.g. TREAT model, surgical population). Some models include the results of FDG-PET imaging and growth on serial imaging.
  - For a given lung nodule, the **probability of malignancy estimate is dependent on the model applied**. In the case presented here the probability could be as low as 37% (Brock model) or as high as 90% (BIMC model) (choice B is correct).

Clinical scenarios		Risk prediction models							
		Gurney	Mayo	Herder	VA	Brock	TREAT	BIMC	Diagnosis
<p>53 yo F, former smoker, 10 pack years. Quit 15 years ago. No emphysema. Smooth RLL 1.2cm module. Hypermetabolic SUVmax 3.3</p>		76%	8%	54.4%	15.2%	6.9%	38%	52%	Necrotizing granuloma
<p>69 yo M, former smoker, 38 pack years. Quit 20 years ago. History of emphysema. Irregular LUL 1.6cm nodule. Hypermetabolic SUVmax 3.2</p>		98%	63%	90%	42.3%	41.2%	73%	85%	Non-small cell carcinoma
<p>54 yo M, active smoker, 58 pack years. History of emphysema. Spiculated RUL 1.4cm nodule. Hypermetabolic SUVmax 12</p>		100%	42%	83%	36.1%	25.3%	69%	97%	Adenocarcinoma
<p>72 yo F, active smoker, 75 pack years. History of emphysema. RUL 6mm nodule found on low-dose CT scan for lung cancer screening. No FDG-PET.</p>		62%	16%	16%	48%	4.2%	68%	12%	Likely benign. Stable for > 2 years.

# Discussion

- When evaluating a solid nodule larger than 8 mm in diameter the management options include **imaging surveillance** (if the nodule has a low probability of malignancy, e.g. < 10%), additional testing with **FDG-PET imaging and/or a non-surgical biopsy** (if the nodule has an intermediate probability of malignancy, e.g. 10-70%), or **surgical resection** (if the nodule has a high probability of malignancy, e.g. > 70%).
- The intermediate probability of malignancy nodules are often the hardest to manage.
  - **FDG-PET imaging** may help to characterize these nodules. A meta-analysis of FDG-PET imaging accuracy suggests this tool is **sensitive (89% sensitivity) but the specificity is more variable (75% overall but 61% in regions with endemic fungal infections)**.
  - Using the 48% pre-test probability, a sensitivity of 89% and specificity of 61% would give a negative predictive value of 85.7%. For a young otherwise healthy patient this may not be quite high enough to justify a surveillance imaging strategy (choice A is incorrect).

## Discussion

- Electromagnetic navigation, ultrathin bronchoscopes, guide sheaths, and peripheral ultrasound techniques have improved the yield above standard bronchoscopy alone or in a complementary fashion.
  - Despite these advances, the **yield for nodules < 2 cm in diameter has been reported to be around 50%** (choice C is incorrect).
- Our patient does not have any symptoms or signs of a lung infection and his nodule does not have features suggesting infection. **Empiric antibiotics are not recommended** in this situation (choice D is incorrect).

# Case 4

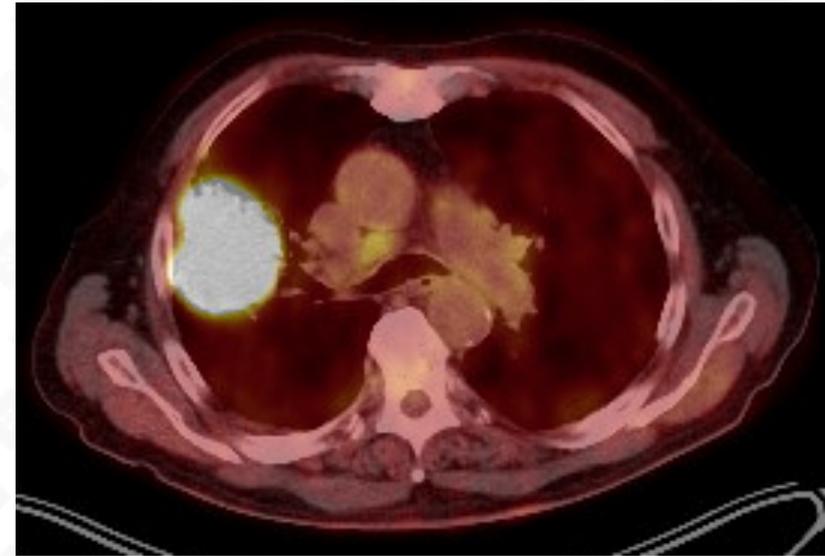


Thailand

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An 88 year old former smoker presented to the emergency department with nausea. He described stable activity limitation from neuropathy related pain. He had a stable chronic cough without sputum production. He described dysphagia to solid foods, 10 lbs. of weight loss over the past 2 months, and one episode of transient diplopia. Imaging performed in the emergency department revealed a 6 cm mass in the right upper lobe and a mildly enlarged right paratracheal lymph node. He underwent EBUS staging of the mediastinum and hila where he was found to have a primary adenocarcinoma of the lung involving the right paratracheal lymph node (station 4R). PET imaging did not show any other suspicious findings. Brain MRI imaging showed a 2 cm lesion compatible with a metastasis.



## Question

What is the clinical stage of this patient's lung cancer?

- A. T2N2M1a – stage IVA
- B. T3N2M1b – stage IVA
- C. T2N2M1b – stage IVB
- D. T3N2M1a – stage IVB

## Discussion

- The latest iteration of the lung cancer staging classification, the **8<sup>th</sup> edition**, has been broadly applied since the start of 2018.
- In the current classification a **6 cm tumor is considered T3** and regional spread to an **ipsilateral mediastinal lymph node is an N2**.
- **M1a** is used when there is a malignant pleural or pericardial effusion, pleural or pericardial nodules, or separate tumor nodules in the contralateral lung. **M1b** is used to describe a single extrathoracic metastasis and **M1c** when there are multiple extrathoracic metastases.
- M1a or M1b are **stage IVA** and M1c is **stage IVB**. Thus this patient's clinical stage is **T3N2M1b which is a stage IVA** (choice B is correct; choices A, C, and D are incorrect).

## Discussion

- Changes from the 7<sup>th</sup> to the 8<sup>th</sup> edition included:
  - The **T category is broken down** by size in 1 cm increments until 5 cm, tumors > 5-7 cm are considered T3 and those > 7 cm T4.
  - Tumors involving the **main bronchus or causing atelectasis** are considered T2a no matter how far from the main carina or how much of the lung is atelectatic, while those that **invade the diaphragm** are labeled T4.
  - The M component now takes into account whether there is a **solitary extra-thoracic metastasis or multiple metastases**.
  - Stages IA, III, and IV have **subdivisions** that were not previously present

Stage	T Category	N Category	M Category
IA1	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T3	N0	M0
	T1-2	N1	M0
IIIA	T4	N0	M0
	T3-4	N1	M0
	T1-2	N2	M0
IIIB	T3-4	N2	M0
	T1-2	N3	M0
IIIC	T3-4	N3	M0
IVA	Any	Any	M1a-b
IVB	Any	Any	M1c

## Discussion

- The clinical stage of lung cancer includes all testing up to surgical resection of the cancer and lymphadenectomy.
- Current guidelines recommend **FDG-PET imaging** as part of staging for all clinical stages of lung cancer, with the exception of ground glass nodules and peripheral clinical stage IA tumors.
  - FDG-PET imaging has been shown to be **more sensitive at detecting occult regional and distant metastases** than CT imaging and bone scanning.
  - As false negatives and false positives do occur, **concerning imaging findings require biopsy confirmation** unless the clinical and imaging presentation suggest overwhelming evidence of wide spread metastases.

## Discussion

- **Endosonographic staging of the mediastinum** and hila is recommended as the first invasive assessment of lymph node metastases in patients with **tumors larger than 3 cm, central tumors, anyone with enlarged hilar or mediastinal lymph nodes on CT imaging, or anyone with increased uptake in the hila or mediastinum on FDG-PET imaging.**
- If the tumor is central, hilar/mediastinal lymph nodes are enlarged, or if there is increased uptake in the hila or mediastinum on FDG-PET imaging, negative endosonographic staging should be **followed by mediastinoscopy.**
- Current guidelines vary in their advice about **brain imaging** as part of staging for individuals without neurologic symptoms.
  - The ACCP guidelines recommend brain imaging for anyone stage III and above while the NCCN recommends MRI of the brain in anyone stage IB and above.

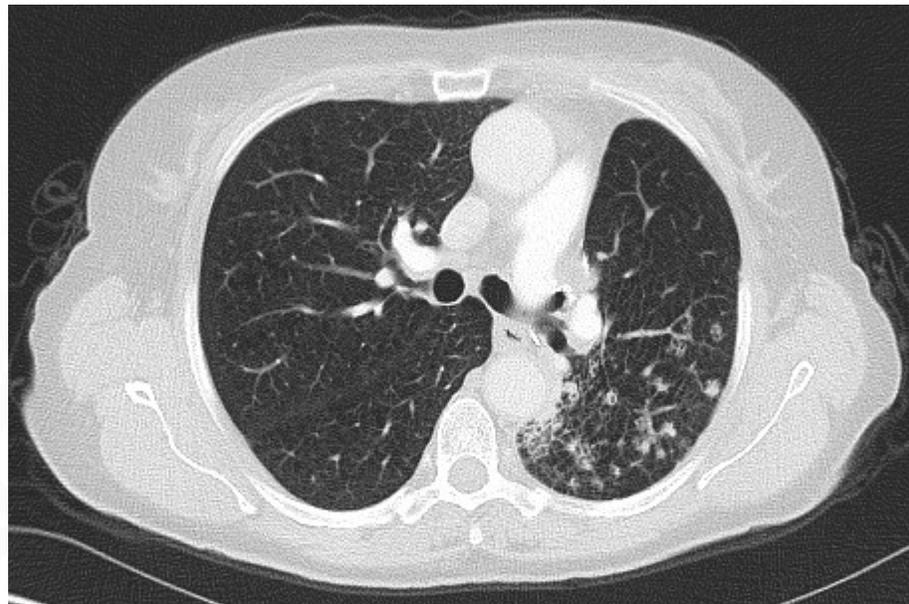
# Case 5



**Thailand**  
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A 68 year old former smoker presents for evaluation of enlarging lung nodules. She has a history of a T2aN0M0 adenocarcinoma of the left upper lobe treated with a left upper lobectomy 5 years ago. Surveillance imaging first identified new small solid nodules in the left lung 2 years ago. Bronchoscopy with sampling of the left lower lobe and EBUS guided staging of the hila and mediastinum did not reveal malignancy. Surgical resection showed multiple foci of adenocarcinoma morphologically consistent with the original adenocarcinoma. Two of the current adenocarcinoma sites and the prior adenocarcinoma had identical Kras mutations. Resected lymph nodes were free of cancer.



## Question

Which of the following features is the strongest indicator that the multiple tumor foci are separate tumor nodules (intrapulmonary metastases) rather than second primary cancers?

- A. They are the same histology.
- B. They have the same radiographic appearance.
- C. They have similar rates of growth.
- D. They have identical Kras mutations.

# Discussion

- It is often difficult to determine if two or more malignant lung nodules are from the same tumor (“separate tumor nodules” or “intrapulmonary metastases”) or are two distinct and unrelated tumors.

Second Primary	Separate Tumor Nodule
<b>Clearly different histology on biopsy</b>	Same histology on biopsy
Different radiographic appearance	Same radiographic appearance
Different biomarker pattern	Same biomarker pattern
Different rates of growth	Similar rates of growth
Absence of nodal or systemic metastases	Significant nodal or systemic metastases
<b>Clearly different by comprehensive histologic assessment</b>	<b>Exactly matching breakpoints by comparative genomic hybridization</b>
<b>Squamous carcinomas arisen from CIS</b>	

# Discussion

	Second Primary Lung Cancer	Multifocal GG/L Nodules	Pneumonic-Type Adenocarcinoma	Separate Tumor Nodule
Imaging features	Two or more distinct masses with imaging characteristic of lung cancer (e.g., spiculated)	Multiple ground glass or part-solid nodules	Patchy areas of ground glass and consolidation	Typical lung cancer (e.g., solid, spiculated) with separate solid nodule
Pathologic features	Different histotype or different morphologic features by comprehensive histologic assessment	Adenocarcinomas with prominent lepidic component (typically varying degrees of AIS, MIA, LPA)	Same histologic features throughout (most often invasive mucinous adenocarcinoma)	Distinct masses with the same morphologic features by comprehensive histologic assessment
TNM classification	Separate cTNM and pTNM for each cancer	T based on highest T lesion with (#/m) indicating multiplicity; single N and M	T based on size or T3 if in single lobe, T4 or M1a if in different ipsilateral or contralateral lobes; single N and M	Location of separate nodule relative to primary site determines if T3, T4, or M1a; single N and M
Conceptual view	Unrelated tumors	Separate tumors, albeit with similarities	Single tumor, diffuse pulmonary involvement	Single tumor, with intrapulmonary metastasis

# Case 6



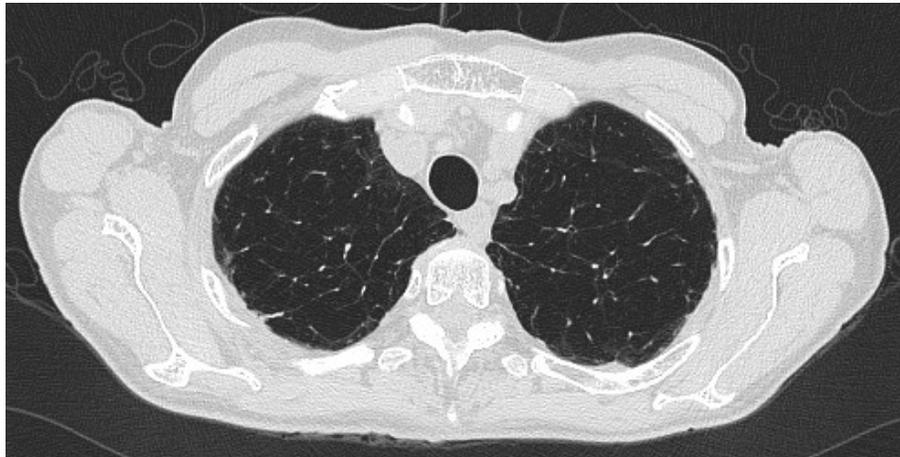
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A 70 year old smoker had chest CT imaging performed in surveillance of a previously treated diffuse large B cell lymphoma. This revealed a left lower lobe lung nodule. PET imaging and guided bronchoscopy have shown a localized adenocarcinoma of the lung without evidence of regional or distant spread.

She currently feels well, exercising regularly without limitation from excessive dyspnea. She has been diagnosed with emphysema and started using maintenance tiotropium within the year. She developed a severe influenza infection 8 months ago. She required hospitalization and was discharged with home oxygen for 3 weeks.

Her chest CT scan shows severe upper zone predominant emphysema with the malignant nodule in the anterolateral aspect of the left lower lobe. There is no adenopathy or pleural disease.



Pulmonary function tests show severe obstruction ( $FEV_1$  0.95L, 45% predicted) and a reduced diffusing capacity (42% predicted). A cardiopulmonary exercise test showed a peak  $VO_2$  of 17 ml/kg/min (80% predicted). There was ventilatory limitation and her  $SpO_2$  fell from 96% on RA at rest to 92% during the test. Thoracic Surgery does not feel that a wedge resection is feasible.

## Question

Which of the following most accurately reflects her risk for pulmonary complications from lung resection?

- A. Her peak  $VO_2$  suggests the risk of complications from lung resection is prohibitive.
- B. Her  $FEV_1$  suggests the risk of complications from lung resection is low.
- C. Her DLCO suggests the risk of complications from lung resection is moderate.
- D. The location of her cancer increases the risk of complications from lung resection.

## Discussion

- The risk of pulmonary complications from lung resection **correlates with the proportion of functional lung that is resected.**
- In this patient with severe, upper zone predominant emphysema, **resection of healthier lung tissue in the lower lobes will lead to a greater reduction in her lung function than if the upper lobes required resection.** This translates into a higher risk of near and long term pulmonary complications (choice D is correct).

# Discussion

**Benefits:** surgery (traditional anatomic, sublobar) vs. SBRT

- Overall survival
- Disease free survival
- Recurrence

**Harms:** surgery (traditional anatomic, sublobar) vs. SBRT

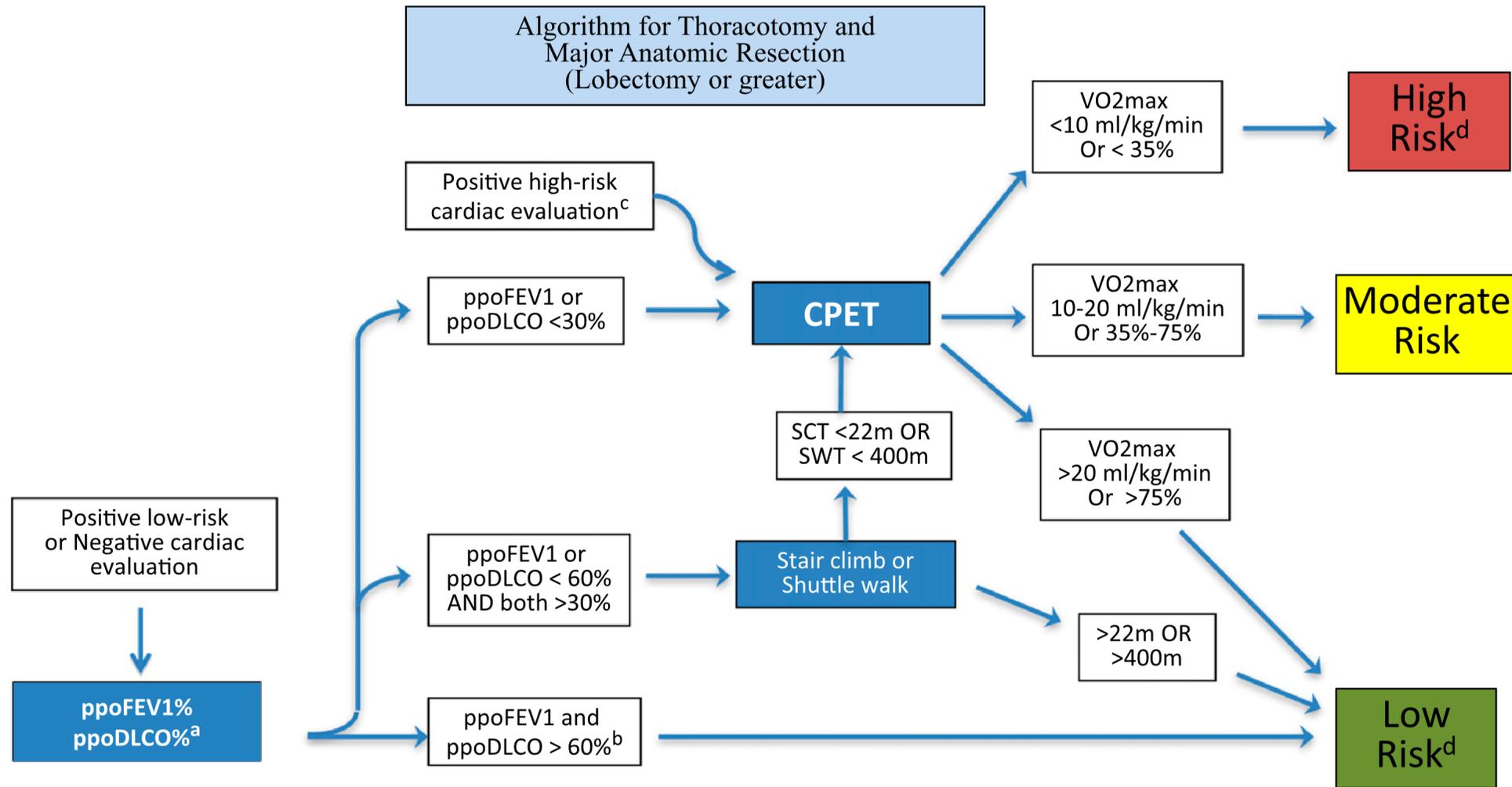
- Mortality
- Morbidity
- Long-term QOL

**Considerations:**

- Size
- Location
- Stage
- Availability

**Considerations:**

- Cardiopulmonary fitness
- Modifying interventions
- Experience
- Surgical approach



## Discussion

- Using this algorithm a peak  $\text{VO}_2$  of 17 ml/kg/min (80% predicted for the patient in this question) would place the patient at **low to moderate risk for complications** (choice A is incorrect).
- The  $\text{FEV}_1$  of 45% predicted would equate to a  $\text{ppoFEV}_1$  of 33-36%, and the DLCO of 42% predicted a  $\text{ppoDLCO}$  of 31-33%, depending on whether a lobectomy or composite basilar segmentectomy was required.
- These values alone are not adequate to assign a level of risk, requiring at least a **low technology exercise test** be performed, though they suggest that the risk is not low (choice B and C are incorrect).

# Case 7

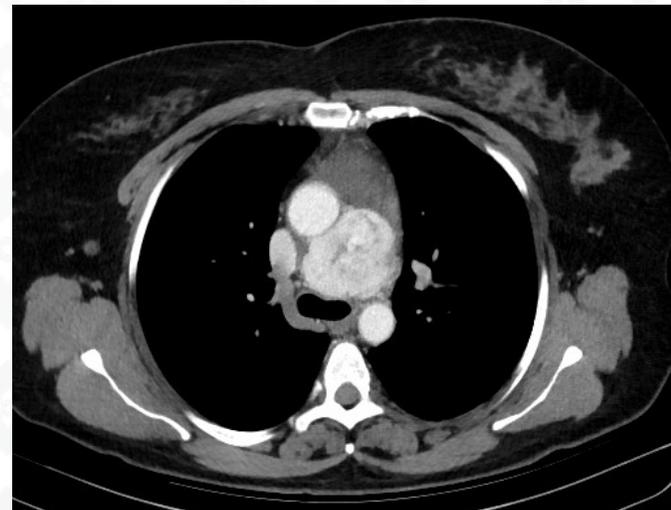
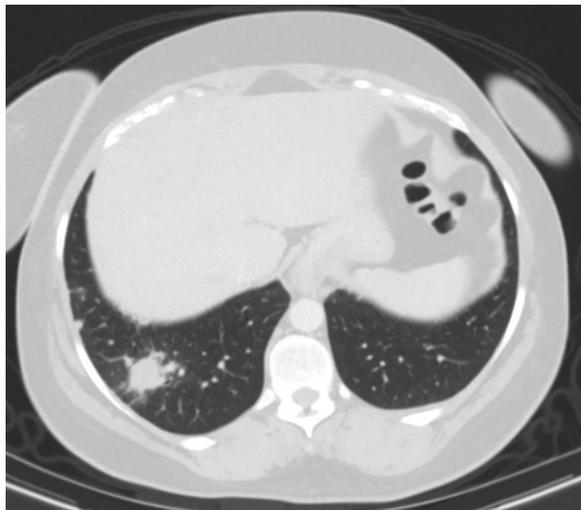


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A 45 year old never smoker describes progressive dyspnea, a non-productive cough, and night sweats unresponsive to oral antibiotics. Chest CT imaging showed a right lower lobe nodule. This led to a transthoracic needle biopsy showing necrotizing granulomas and *Histoplasma capsulatum* yeast forms. She was treated with itraconazole with initial improvement of her symptoms. She then began to develop tingling in her arms, progressive dyspnea, and central chest heaviness. An echocardiogram was performed showing a moderate sized pericardial effusion. She was admitted to the hospital for further evaluation. Her chest CT scans were reviewed.



## Question

Which of the following is the most likely cause of her middle mediastinal mass?

- A. Histoplasmosis
- B. Paraganglioma
- C. Hodgkin's lymphoma
- D. Bronchogenic cyst

## Discussion

- The mediastinal windows of the chest CT with contrast show an **enhancing mass in the middle mediastinum**. Paragangliomas can diffusely enhance on CT imaging (choice B is correct) while none of the other conditions listed as responses do (choices A, C, and D are incorrect).
- The **middle mediastinum** contains the heart, pericardium, ascending and transverse portions of the aorta, superior vena cava, phrenic and upper vagus nerves, trachea and main bronchi, pulmonary artery and its main branches, pulmonary veins, and lymph nodes.
- The most common middle mediastinal masses belong in one of three “A” categories – **adenopathy, aneurysm, and abnormalities of development**. Many other less common causes have been reported.

## Discussion

- **Hypervascular masses** that involve the middle mediastinum include angiofollicular lymph node hyperplasia (Castleman's disease), vascular malformations, metastatic disease, and paragangliomas.
  - Hypervascular lymph node metastases usually originate from **hypervascular tumors** (e.g. renal cell carcinoma, melanoma, thyroid carcinomas, and neuroendocrine tumors).
- Hypervascular masses in other mediastinal compartments include the above plus ectopic parathyroid adenomas and thymic carcinoids (anterior mediastinum) and neurogenic tumors (posterior mediastinum).

# Discussion

- Paragangliomas arise from **chromaffin cells in the adrenal glands and from extraadrenal neuroendocrine tissues**. In the adrenal glands they are known as **pheochromocytomas**.
- Mediastinal paraganglia are present in the **aortic body and in the aortopulmonary window** in the middle mediastinum (bronchiomeric paraganglia including the aortopulmonary paraganglia), and along the **sympathetic trunk** in the posterior mediastinum (aortosympathetic paraganglia).
  - Paragangliomas arising in the **middle mediastinum** are more likely to be asymptomatic and occur in those over 40 years old. Their presentation is delayed until they develop **chest pain or shortness of breath due to compression of nearby structures**. They are typically located **adjacent to the great vessels**. They homogeneously and avidly enhance on CT imaging when small and may be more heterogeneous when larger.
  - Those in the **posterior mediastinum** more often present with **symptoms and testing similar to an adrenal pheochromocytoma**.

# Case 8

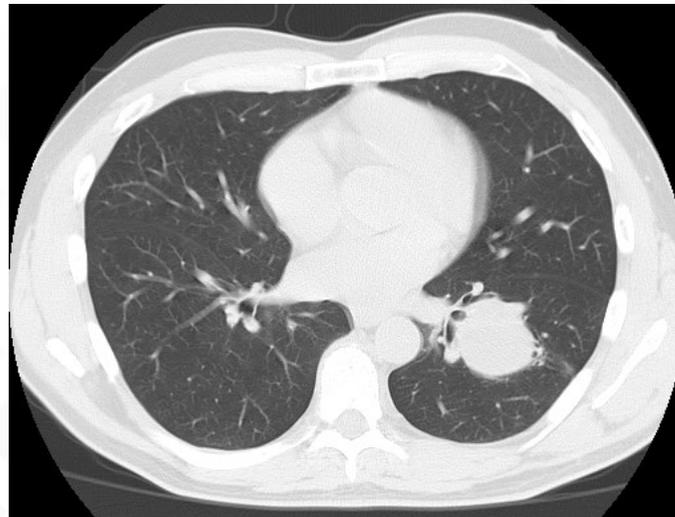
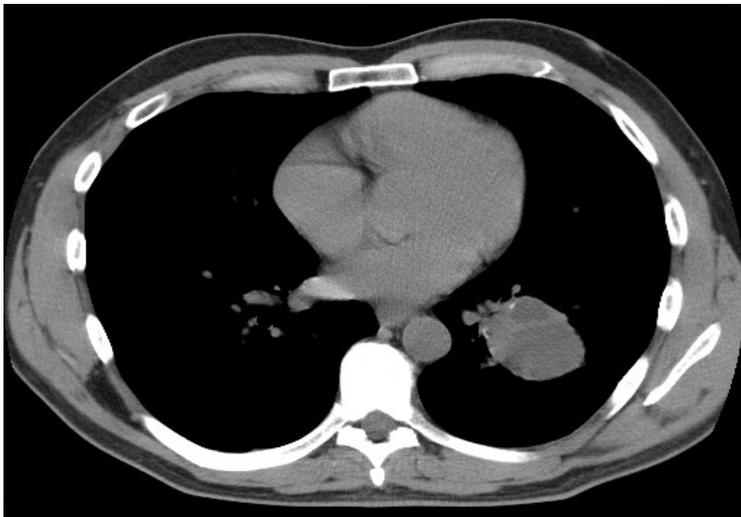


**Thailand**  
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A 48 year old male never smoker presents with a chronic non-productive cough and malaise. He is otherwise very healthy, able to be active without other cardiopulmonary or systemic symptoms. He has not had known worrisome exposures. There is no family history of malignancy.

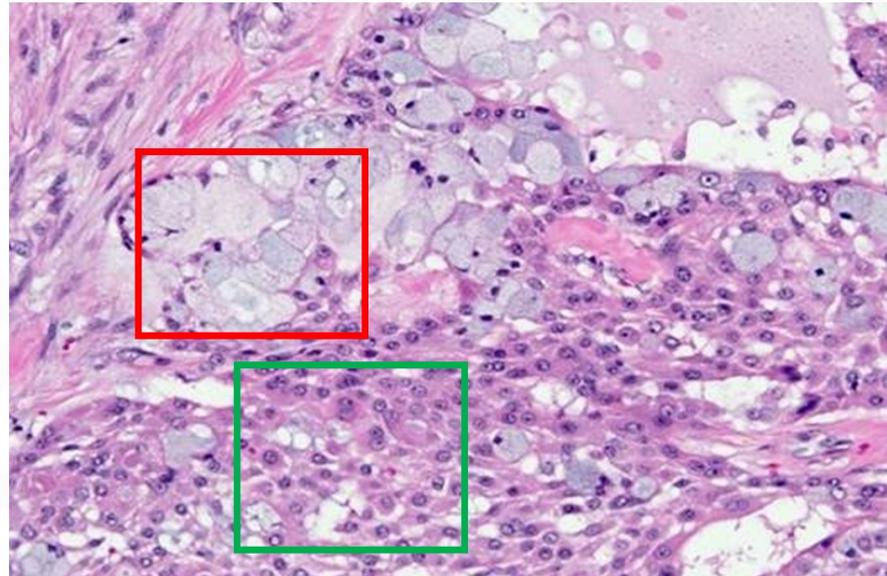
A chest x-ray then chest CT scan was obtained showing a 5 cm mass in the left lower lobe. Bronchoscopy was performed to obtain a diagnosis. An endobronchial component of the mass was seen in the lateral basal segment of the left lower lobe. The biopsy was found to have the fusion transcript  $t(11;19)(q21;p13)$ .



## Question

This tumor is most likely to be:

- A. a pleomorphic adenoma.
- B. a mucoepidermoid carcinoma.
- C. an adenoid cystic carcinoma.
- D. an adenosquamous cell carcinoma



## Discussion

- Mucoepidermoid carcinoma is the **most common type of pulmonary salivary gland tumor**.
- It can be found from the trachea to the peripheral lung and can grow to be large.
- Most often, it is well defined and has an endobronchial component in the **trachea or main bronchi**.
- The median age of presentation is 45 years and there is a slight male predominance.
- Cytologic features allow mucoepidermoid carcinomas to be divided into low (the majority) - and high-grade variants.
- Lymph node involvement is uncommon.
- Treatment of mucoepidermoid carcinomas (and other pulmonary salivary gland tumors) is **surgical resection when possible**. Low grade tumors have a very good prognosis while the prognosis of those with high grade tumors can be poor.

## Discussion

- Pulmonary **mucoepidermoid carcinomas**, particularly when high grade, can be **difficult to distinguish from adenosquamous** cell carcinomas of the lung.
  - Tumor location (more peripheral for adenosquamous carcinomas) and the presence of a low-grade mucoepidermoid component within the tumor can help to separate the two (choice D is incorrect).
  - Histologically they can be distinguished by the presence of **mucus secreting, squamous, and intermediate cells** in a variety of architectural patterns.
  - The **fusion transcript** t(11;19)(q21;p13), between the mucoepidermoid carcinoma translocated 1 (MECT1) gene on chromosome 19p13 and mastermind-like 2 (MAML2) on chromosome 11q21 has recently been identified in most pulmonary mucoepidermoid carcinomas (choice B is correct).

# Discussion

- **Pleomorphic adenomas** are the most common type of salivary gland tumor in the head and neck but are very rare in the lungs.
  - They can be central or peripheral and can grow to be very large.
  - Mucus and mucus secreting cells are not seen histologically (choice A is incorrect).
- **Adenoid cystic carcinomas** are the second most common pulmonary salivary gland tumor.
  - They most often arise in the large airways, are usually smaller than 4 cm, and are more common in men.
  - They may be less distinct and more infiltrative, invading and growing along perineural spaces, the bronchial mucosa, and airway cartilage.
  - They may be characterized by a t(6;9) (q22-23;p23-24) translocation leading to fusion between a v-myb avian MYB viral oncogene homolog and nuclear factor 1B (choice C is incorrect).

# Case 9



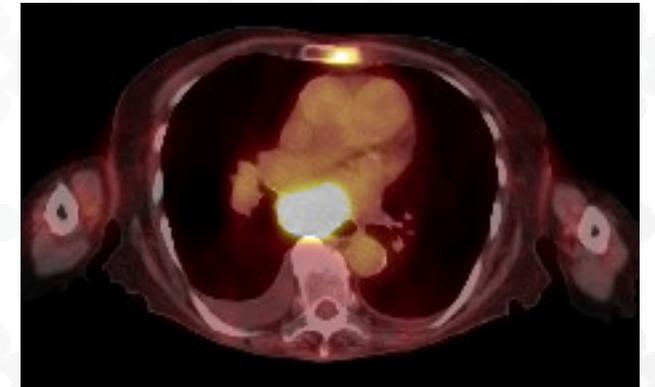
**Thailand**  
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An 81 year old never smoker describes increasing fatigue, dyspnea with activities, and a non-productive cough. She is known to have scleroderma, pulmonary hypertension, and sleep apnea. Chest CT imaging performed to evaluate her symptoms showed bilateral solid lung nodules and mediastinal adenopathy. PET/CT imaging identified the nodules, adenopathy, and a sternal lesion as being FDG avid. A needle biopsy of the sternal lesion revealed scant malignant cells compatible with a non-small cell carcinoma.

Which of the following is the best next step?

- A. EBUS guided sampling of the mediastinal adenopathy.
- B. Treatment with osimertinib.
- C. Blood testing for EGFR mutations.
- D. Treatment with platinum doublet chemotherapy plus an immune checkpoint inhibitor.



## Discussion

- The selection of treatment for advanced stage non-small cell lung cancer is contingent on **accurate molecular characterization** of the cancer.
  - **EBUS** guided bronchoscopy has been shown to be able to **provide enough tissue for molecular testing**. Given the large subcarinal lymph node, the next step would be EBUS guided sampling of the mediastinal adenopathy (choice A is correct).
- Adenocarcinoma and squamous cell carcinoma responded differently to **traditional chemotherapy regimens**.
- Some non-squamous cell lung cancers contain **molecular alterations that drive tumor growth**. Treatment of patients identified as having certain activating alterations (e.g. EGFR, ALK, ROS1) with targeted tyrosine kinase inhibitors (TKI) has been shown to improve survival and quality of life (e.g. osimertinib, a third generation EGFR inhibitor).
  - These treatments are **not effective if the molecular alteration is not present** (choice B is incorrect).

## Discussion

- Some lung cancers evade the body's immune system by activating **immune checkpoints**, natural mechanisms that regulate the body's immune response.
  - Immune checkpoint inhibitor (ICI) therapy has been shown to improve survival as a stand-alone therapy when the cancer displays high **expression of programmed death ligand 1** (> 50% of cancer cells) and in combination with traditional platinum doublet chemotherapy in stage 3 and 4 patients without targetable driver mutations even when PDL-1 expression is low (choice D is incorrect).
  - It is now recommended that all non-small cell cancers have PDL-1 testing performed. Additional markers of response to ICI therapy are being evaluated (e.g. tumor mutational burden).
- When tissue is not able to be obtained due to tumor location or patient health, liquid biopsies (i.e. blood tests that evaluate circulating cell-free DNA) can be considered (choice C is incorrect).

# Molecular Testing Guidelines

	Stand Alone	Panel
<b>EGFR</b>	X	X
<b>ALK</b>	X	X
<b>ROS1</b>	X	X
<b>BRAF</b>	X	X
<b>RET</b>		X
<b>ERBB2</b>		X
<b>KRAS</b>		X
<b>MET</b>		X

**Table 5. Emerging Markers for Molecular Testing in Lung Cancer**

Mitogen-activated protein kinase kinase 1 (*MEK1/MAP2K1*)  
 Fibroblast growth factor receptor 1–4 (*FGFR 1–4*)  
 Neurotrophic tyrosine kinase, receptor, type 1–3 (*NTRK1-3*)  
 Neuregulin 1 (*NRG1*)  
 Ras-like without CAAX 1 (*RIT1*)  
 Neurofibromin 1 (*NF1*)  
 Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*)  
 AKT serine/threonine kinase 1 (*AKT1*)  
 NRAS proto-oncogene, GTPase (*NRAS*)  
 Mechanistic target of rapamycin (*MTOR*)  
 Tuberous sclerosis 1 (*TSC1*)  
 Tuberous sclerosis 2 (*TSC2*)  
 KIT proto-oncogene receptor tyrosine kinase (*KIT*)  
 Platelet-derived growth factor receptor alpha (*PDGFRA*)  
 Discoidin domain receptor tyrosine kinase 2 (*DDR2*)

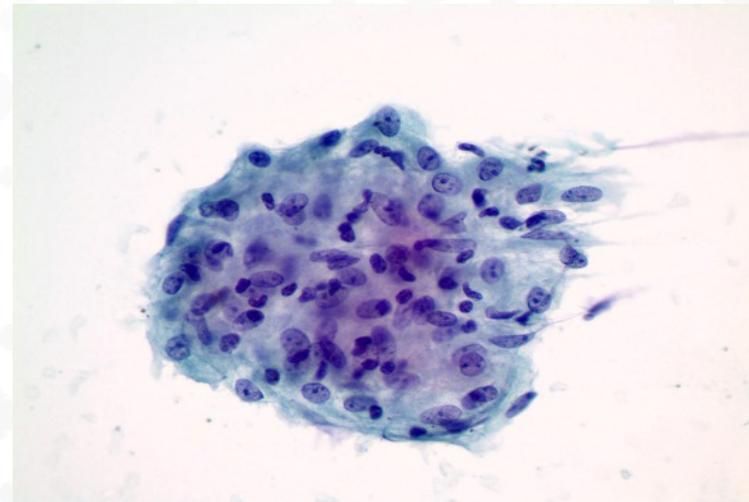
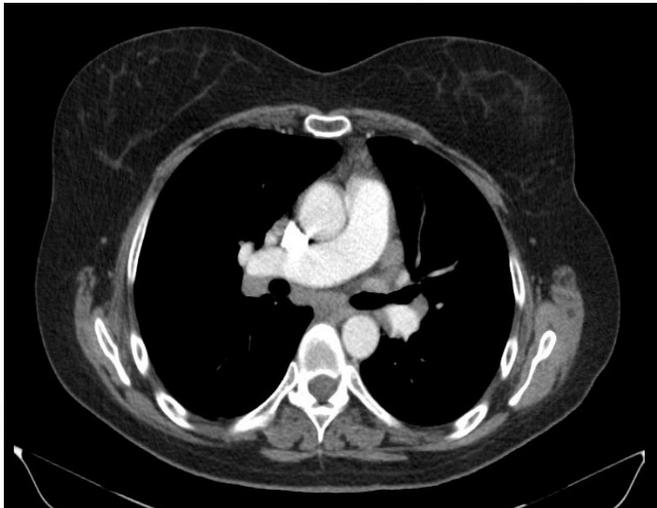
# Case 10



**Thailand**  
Bangkok | 10-12 April



A 47 year old former smoker is seen for evaluation of mediastinal and hilar adenopathy. She was diagnosed with a stage IIIB malignant melanoma of the left hip approximately 6 months ago. In addition to resection she has been treated with the immune checkpoint inhibitor pembrolizumab. Approximately 3 months into her treatment she presented with fatigue, weakness, and generalized aches. Imaging including a chest CT was performed. The chest CT showed new mediastinal and bilateral hilar adenopathy without any abnormal parenchymal findings. She underwent EBUS guided bronchoscopy with sampling of these lymph nodes.



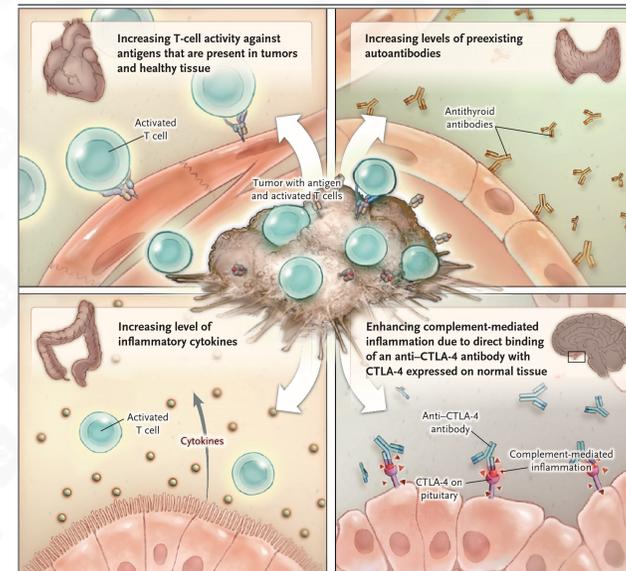
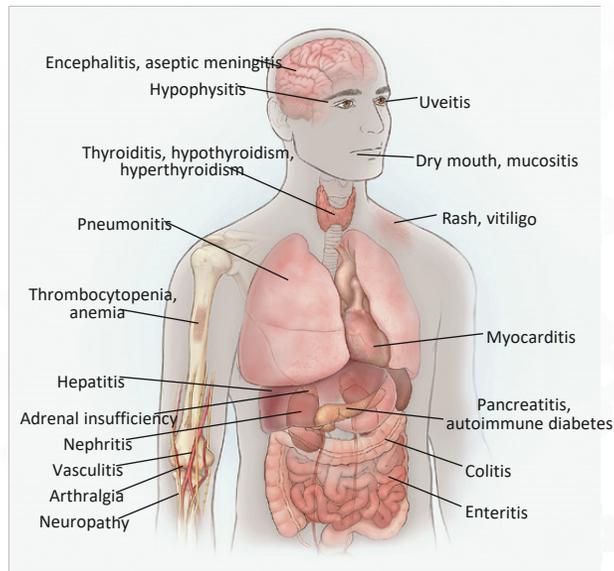
## Question

Which of the following best fits her presentation?

- A. An immune related adverse event
- B. Metastases from her melanoma
- C. Histoplasmosis
- D. Tuberculosis

# Discussion

- The presentation of **symmetric hilar and mediastinal adenopathy** without parenchymal findings and a biopsy that shows **non-necrotizing granulomas** favors sarcoidosis over fungal and mycobacterial infections. Malignant cells are not present on her biopsy. **Sarcoidosis like reactions have been reported in patients receiving immune checkpoint inhibitor therapy** (choice A is correct; choices B, C, and D are incorrect).



# Discussion

- **Pulmonary toxicity** occurs in 2.7-3.5% of patients treated.
  - Combined treatment with radiation, driver mutation targeted therapy, or a second ICI increases the risk of pulmonary toxicity, as does the presence of an underlying inflammatory or fibrotic lung disease.
- The presentation of pneumonitis includes **non-specific respiratory and systemic symptoms and a variety of imaging findings** (consolidations, ground glass opacities, interlobular septal thickening, lung nodules, bronchiectasis, and pleural effusions).
- Biopsy findings can be similar to **drug induced pneumonitis** with inflammatory and lymphocytic infiltration.
  - Biopsies can reveal cellular non-specific interstitial pneumonitis, cryptogenic organizing pneumonia, acute interstitial pneumonitis, hypersensitivity pneumonitis, or bronchiolitis.
  - In addition, mediastinal and symmetric hilar adenopathy with a **sarcoid-like granulomatous reaction** has been reported.

Grading	Management
<p><b>1:</b> Aysmptomatic, confined to one lobe of the lung or &lt; 25% of lung parenchyma</p>	<p>Hold ICPI with radiographic evidence of pneumonitis progression            May offer repeat CT and PFTs in 3-4 weeks            May resume ICPI with radiographic improvement; if no improvement then treat as G2            Monitor weekly</p>
<p><b>2:</b> Symptomatic, involves more than one lobe of the lung or 25-50% of lung parenchyma</p>	<p>Hold ICPI until resolution to G1 or less            Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks            Consider bronchoscopy with BAL, empiric abx            Monitor q3 days, treat as G3 if no improvement after 48-72 hours of prednisone</p>
<p><b>3:</b> Severe symptoms, hospitalization required, involves all lung lobes or &gt; 50% of lung parenchyma, limiting self-care ADL, oxygen indicated</p> <p><b>4:</b> Life-threatening respiratory compromise, urgent intervention indicated</p>	<p>Permanently discontinue ICPI            Empiric abx, methylprednisolone IV 1-2 mg/kg/d            If no improvement after 48 hrs may add infliximab 5 mg/kg or mycophenolate IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks            Bronchoscopy with BAL +/- TBBx</p>

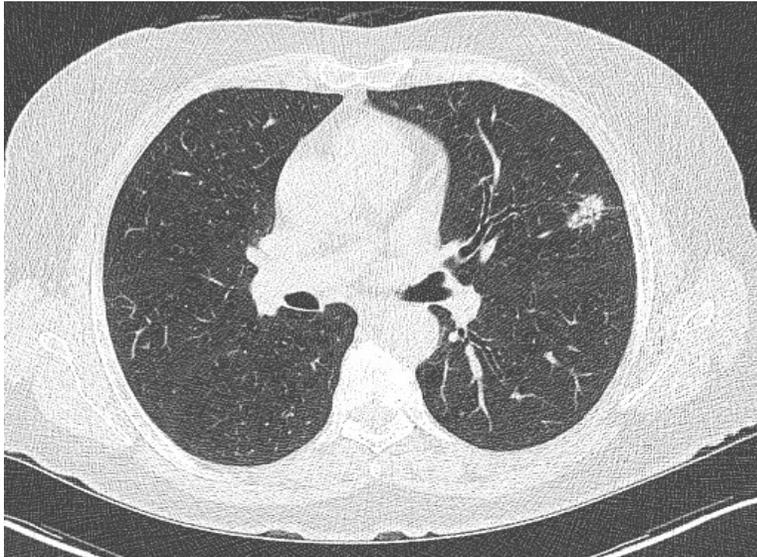
# Case 11



Thailand  
Bangkok | 10-12 April



A 60 year old former smoker presented for a lung cancer screening shared decision making visit. She elected to proceed with the low-dose chest CT. This revealed a category 4B nodule in the left upper lobe. FDG-PET imaging showed uptake in the lung nodule (SUV 6.1) and in a left adrenal nodule (SUV 11.1). There was no concerning uptake elsewhere. A biopsy of the adrenal nodule showed adenocarcinoma of lung primary, K-ras mutant with 10% PDL-1 staining cancer cells. A brain MRI scan did not show any metastases. She is currently active without cardiopulmonary or systemic symptoms. Spirometry and diffusing capacity measurements are normal.



## Question

What is the most appropriate next step?

- A. Platinum doublet chemotherapy plus an immune checkpoint inhibitor.
- B. Surgical resection of the left upper lobe and left adrenal gland.
- C. Treatment with brigatinib.
- D. Invasive staging of the mediastinum.

## Discussion

- This patient presents with a T1bN0M1b, **stage IVA adenocarcinoma** of the lung, based on a **single metastatic site in the left adrenal gland**.
- A minority of patients with stage IV non-small cell lung cancer present with a solitary metastasis. These patients have an **overall better survival than patients with multiple metastases in one or several organs**, and similar survival to those with metastases within the thorax.
  - For this reason, the current staging classification has separated M descriptors to include M1a (metastases within the thorax), M1b (a single metastasis in a single organ), and M1c (multiple metastases in one or several organs).
  - Those with M1a or M1b are grouped as a stage IVA and those with M1c are stage IVB.

## Discussion

- With a single metastasis to the brain or adrenal gland, **curative intent resection followed by adjuvant chemotherapy should be considered.**
  - This treatment paradigm only applies when there is **no evidence of regional metastases to the mediastinal lymph nodes.**
  - Despite the absence of suggestion of regional spread on imaging tests it is recommended that **invasive staging of the mediastinum** be performed prior to deciding on a treatment plan (choice D is correct, choices A, B, and C are incorrect).
  - Platinum doublet chemotherapy plus an immune checkpoint inhibitor would be considered standard of care for those with multiple metastases, no targetable driver mutations, and PDL-1 staining in < 50% of cancer cells.
  - Brigatinib is appropriate first line treatment for lung cancer with an identified anaplastic lymphoma kinase mutation.

# Case 12



**Thailand**  
Bangkok | 10-12 April



## Question

Which of the following statements about the components of a high-quality lung cancer screening program is true?

- A. A low dose chest CT scan delivers the same amount of radiation as a standard chest radiograph.
- B. Lung nodules are the only actionable findings identified by the low dose chest CT scan.
- C. Shared decision making refers to decisions made by a family member for the individual being screened.
- D. Higher smoking cessation rates improve the cost-effectiveness of lung cancer screening.

## Discussion

- **Increasing the rate of smoking cessation** in a lung cancer screening program can improve the cost-effectiveness of lung cancer screening (choice D is correct).
- Screening, by definition, is performed in healthy individuals. A minority of those screened will experience the benefit of screening while all are exposed to the potential harms.
- A favorable balance of benefit and harms requires screening be performed in high quality settings.

## Discussion

- Lung cancer screening studies have reported **variable results on the impact that participating in lung cancer screening has on smoking cessation rates**. Most have reported no change (for the better or worse) while one has suggested increased cessation rates.
- It is important to use low radiation dose techniques when performing a screening CT, and when following screen detected lung nodules, in order to **minimize the potential risk of radiation** from serial chest CT imaging.
  - A low radiation dose chest CT ( $< 3.0 \text{ mGy CTDI}_{\text{vol}}$ ) delivers approximately 10 times the radiation of a chest radiograph and  $1/5^{\text{th}}$  the radiation of a diagnostic chest CT (choice A is incorrect).

## Discussion

- The screening CT scan **identifies lung nodules in the majority of individuals screened**. The rate of a positive findings varies with the nodule size used as a threshold for a positive study.
- **Non-nodule imaging findings are common**. Examples of potentially actionable findings include coronary artery calcification, thyroid nodules, adrenal nodules, aortic aneurysms, and emphysema (choice B is incorrect).
- **Shared decision making** has been defined as a “collaborative process that allows patients and their health care providers to make health care decisions together, taking into account the best scientific evidence available, as well as the patient’s values and preferences” (choice C is incorrect).