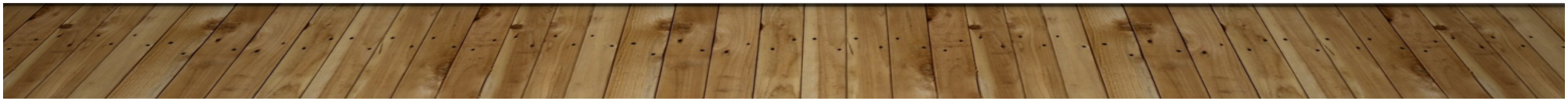
LUNG CANCER UPDATES

TAGHI RIAHI; M.D.

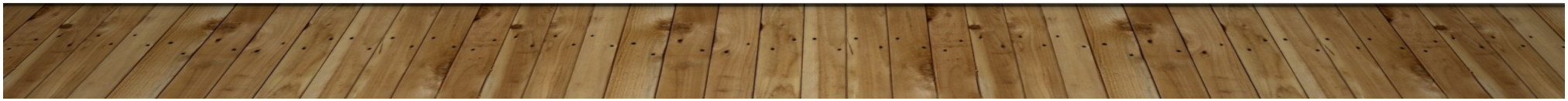
- Most patients with lung cancer present for diagnostic evaluation because of suspicious symptoms or an incidental finding on chest imaging.

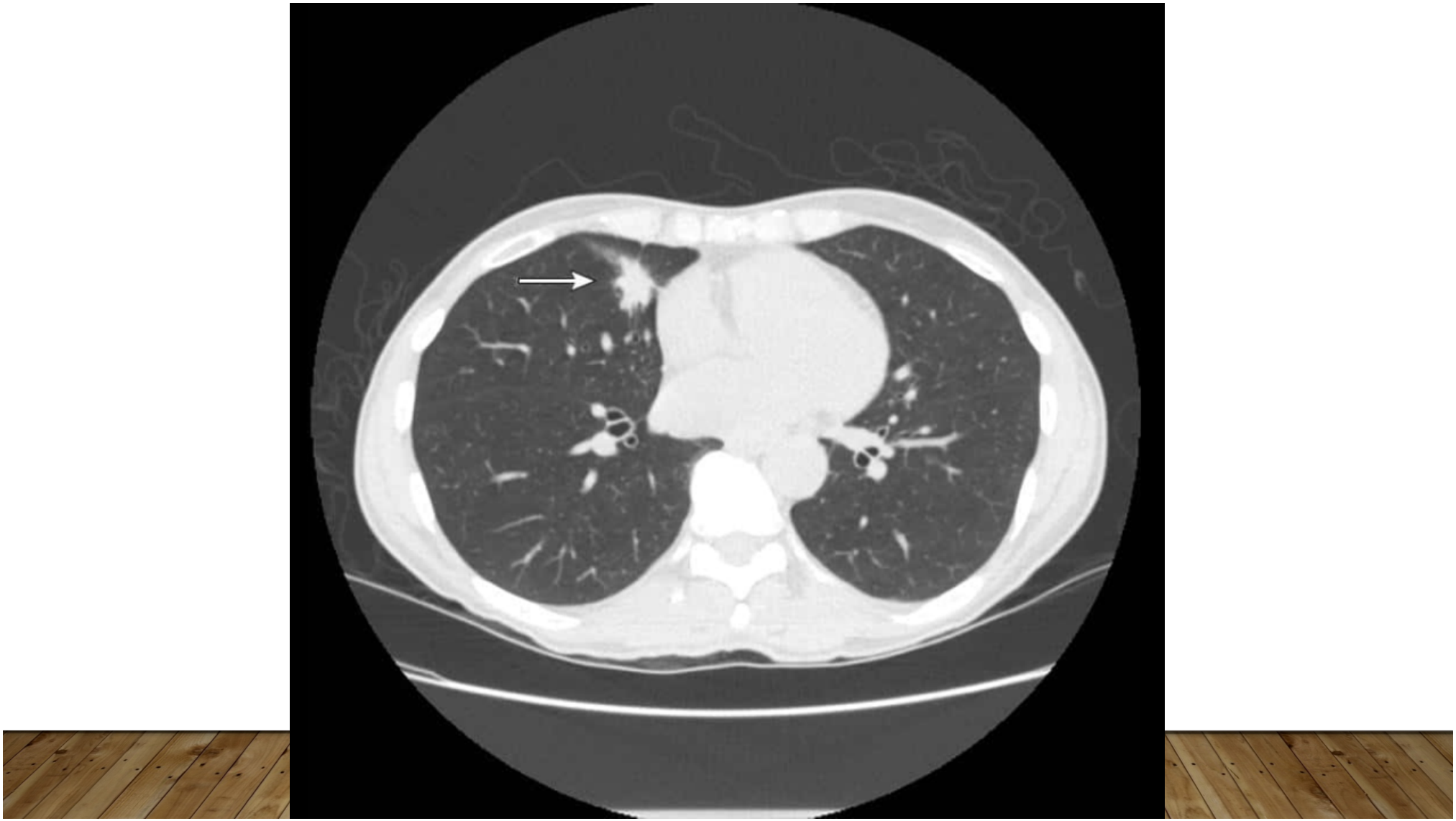
- The goal of the initial evaluation is to obtain sufficient clinical and radiologic information to guide diagnostic tissue biopsy, staging, and treatment.

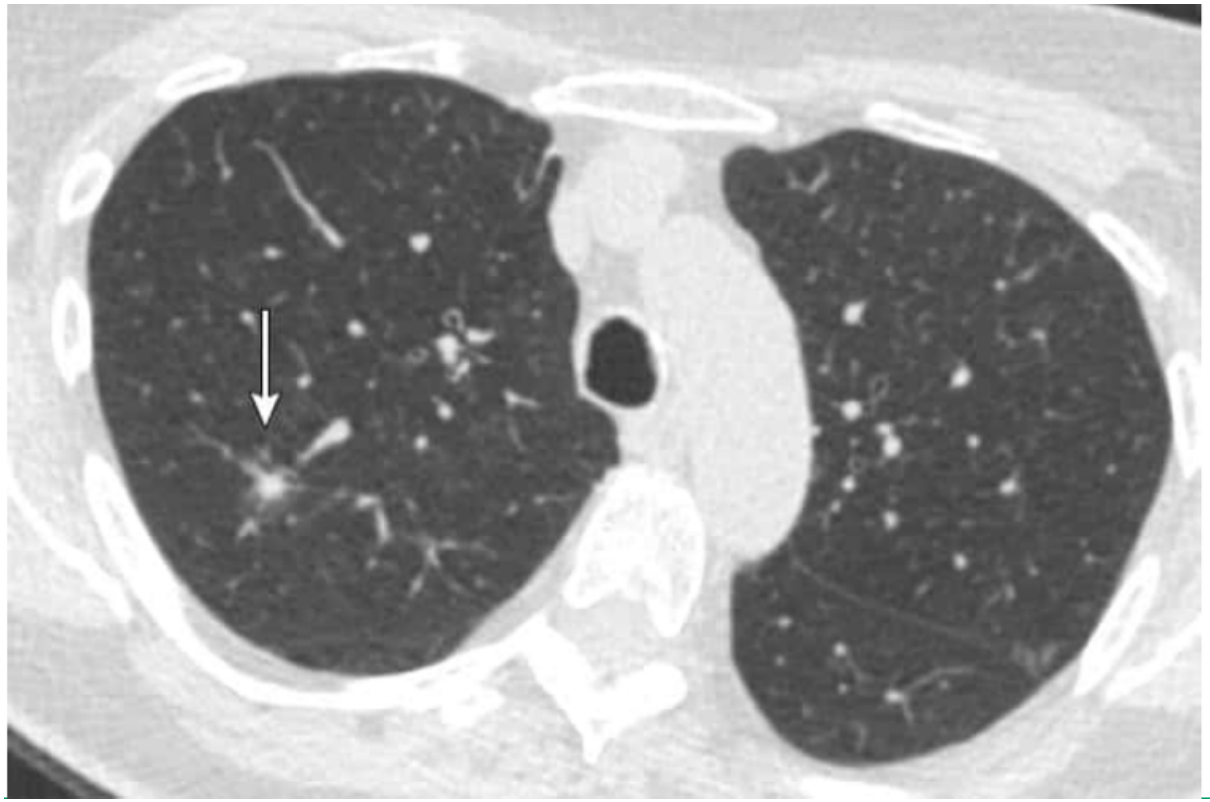


SOLITARY PULMONARY NODULE

- A pulmonary nodule is defined on imaging as a small (≤30 mm), well-defined lesion surrounded by pulmonary parenchyma

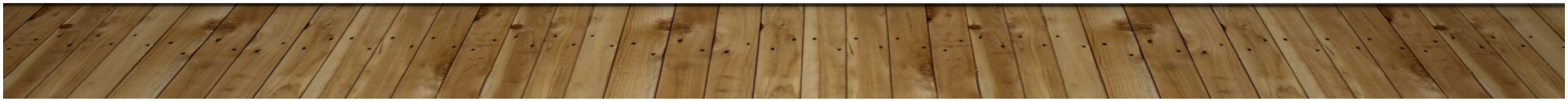






ASSESSING THE RISK OF MALIGNANCY

- Low probability (<5 percent)
- Intermediate probability (5 to 65 percent)
- High probability (>65 percent)



Input

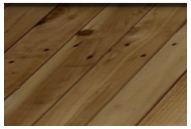
Age		years ▼
Sex	○ Female (0.6011)	
	○ Male (0)	
Family history of lung cancer	☐ (0.2961)	
Emphysema	☐ (0.2953)	
Nodule size		mm ▼
Nodule type	○ Nonsolid or ground-glass (-0.1276)	
	○ Partially solid (0.377)	
	○ Solid (0)	
Nodule in upper lung	☐ (0.6581)	
Nodule count		# ▼
Spiculation	☐ (0.7729)	

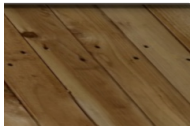
Results

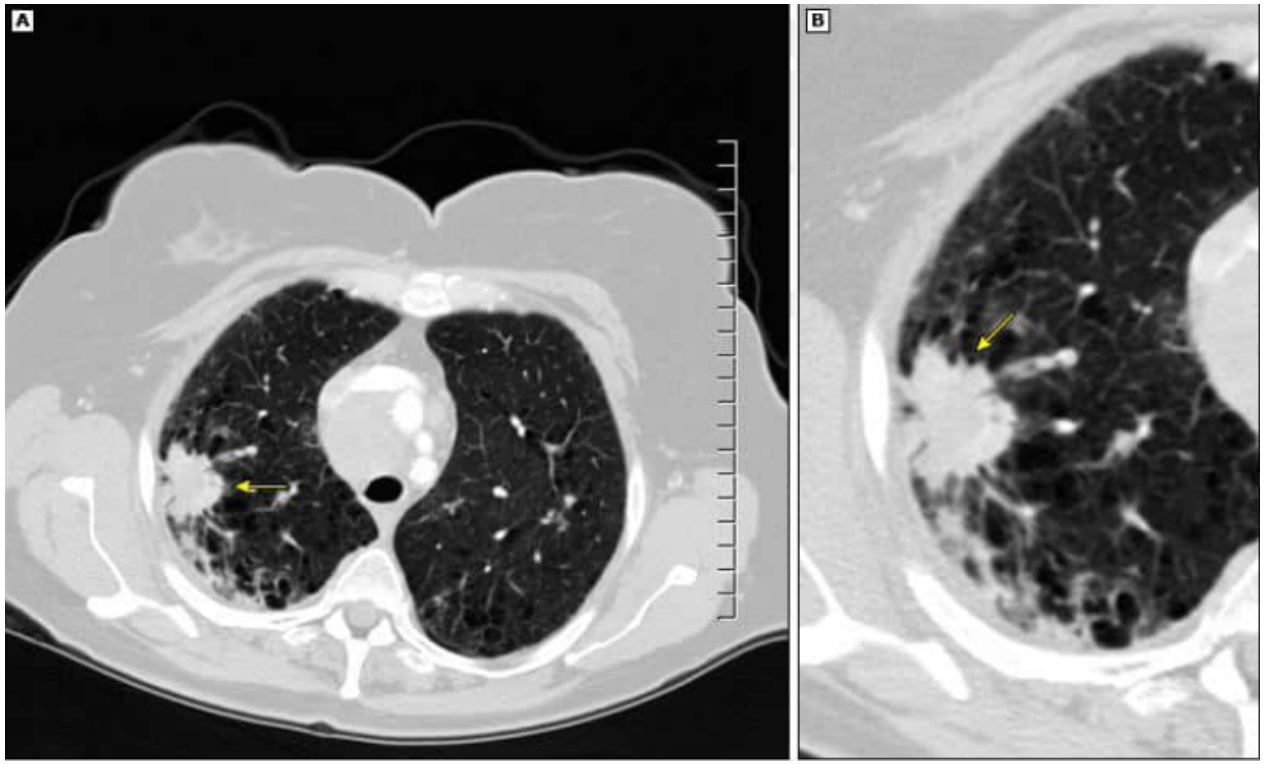
Important: Inputs must be complete to perform calculation.

Log odds		
Cancer probability		% ▼

Decimal precision 2 ▼

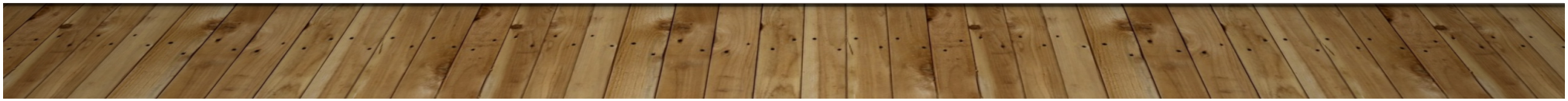




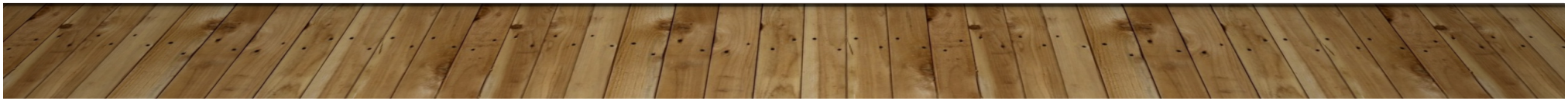

A
B

- Although no single quantitative predictive model is superior, they all combine clinical and imaging features to estimate the probability of malignancy

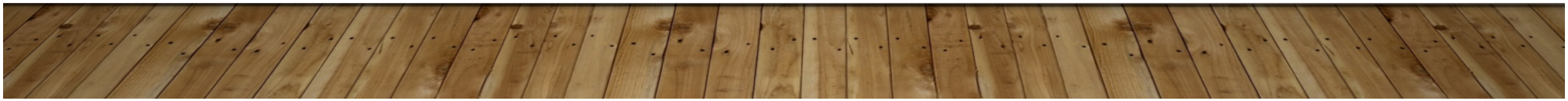
- They are most useful for nodules that are 8 to 30 mm to facilitate patient discussion and guide management choices



- Typically, lesions >30 mm that lack benign features are resected because they have such a high likelihood of malignancy that the benefit of resection outweighs the associated risk of surgery.



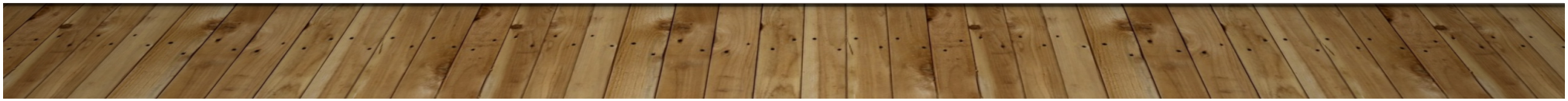
- Predictors of cancer were identified in 2961 patients with nodules found on first screening CT and included the following: older age, female sex, family history of lung cancer, emphysema, larger nodule size, location of the nodule in the upper lobe, part-solid nodule type, lower nodule count, and speculation



ATTENUATION

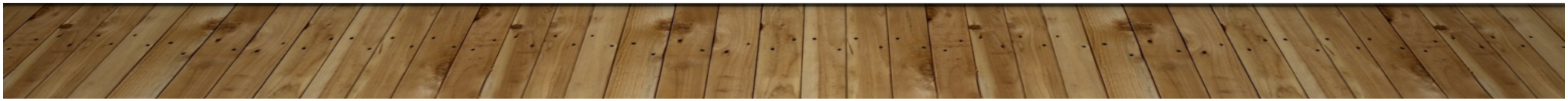
- Solid nodules – Solid nodules are typically dense and homogeneous on imaging. Solid nodules ≤8 mm (also known as "sub centimeter" nodules) are less likely to be malignant, are difficult to biopsy, not reliably characterized by functional imaging, and, hence, best characterized with CT surveillance.

- By contrast, solid nodules >8 mm have a greater likelihood of malignancy, can be more reliably characterized by functional imaging (i.e., PET), and are more likely to be successfully diagnosed by biopsy



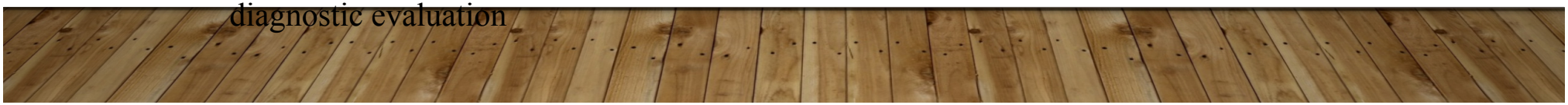
- Subsolid nodules are pulmonary nodules that are pure ground-glass nodules or are part-solid ground-glass nodules.

- The incidence of subsolid nodules is increasing, likely due to the rising incidence of adenocarcinoma worldwide and the increasing use of CT. The most common histologies seen with ground-glass morphology are atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and minimally invasive adenocarcinoma (MIA)



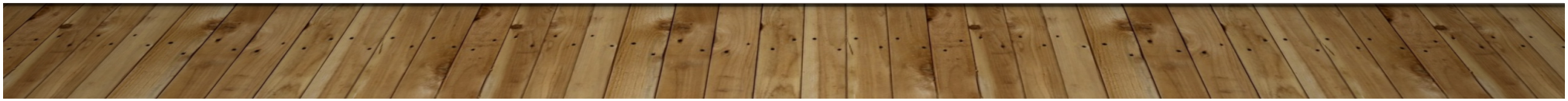
GROWTH OR STABLE SIZE

- For solid nodules, growth is defined as an increase in size of >2 mm
- For subsolid nodules, growth can also be identified as an increased attenuation or an increase in the size of or development of a solid component
- Compared with chest radiography, CT can better detect changes in diameter (0.5 mm change versus 3 to 5 mm) .
- A solid nodule that has been stable by CT for at least two years does not need any further diagnostic evaluation



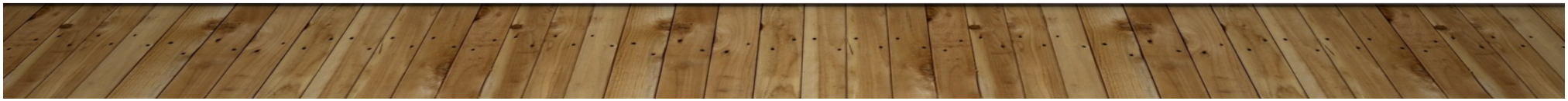
- Studies that assess the volume doubling time (VDT) of cancers have been helpful in predicting the probability of malignancy in a pulmonary nodule. Most malignant nodules have a VDT between 20 and 400 days, with slower VDTs (>400 days) observed in typical carcinoid and in preinvasive or low grade adenocarcinoma (eg, adenocarcinoma in situ [AIS] and minimally invasive adenocarcinoma [MIA]) .

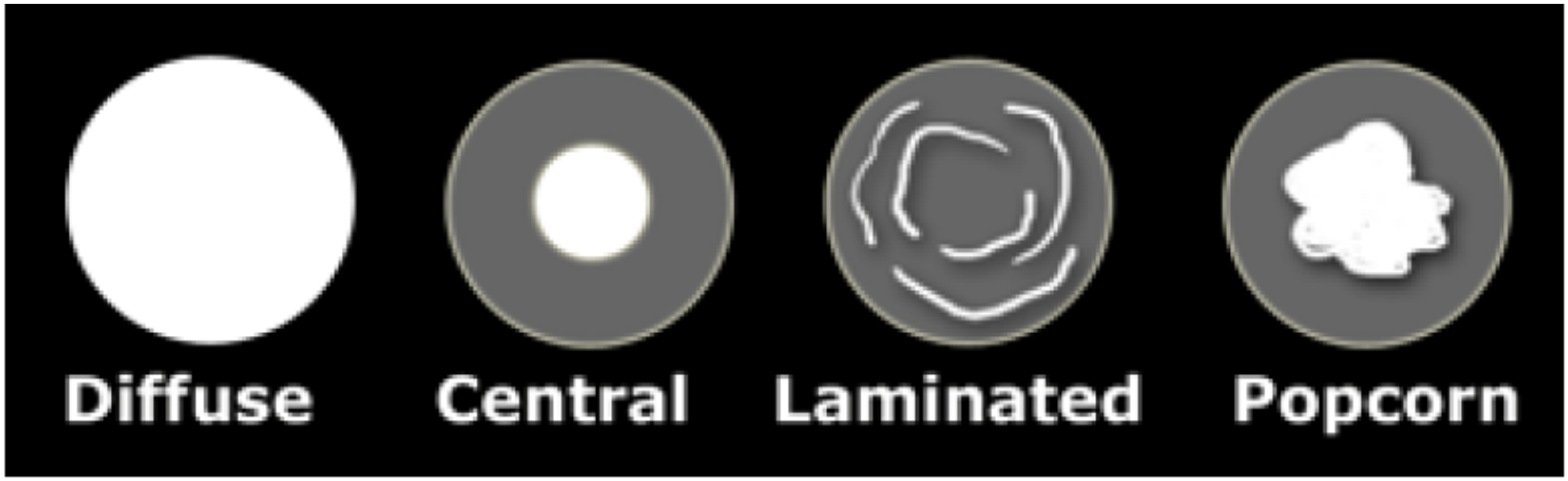
- Thus, a nodule that has increased in size over a short period of time (<20 days) or is stable for a prolonged period on CT (>2 years) is likely benign



CALCIFICATION AND FAT

- There are four benign patterns of calcification, which are central, diffuse, lamellated, and "popcorn.
- Central, diffuse, and lamellated are typically seen with prior infection, particularly histoplasmosis or tuberculosis.
- Popcorn calcification is characteristic of chondroid calcification in a hamartoma.
- However, lung cancers, typical and atypical pulmonary carcinoid tumors occasionally show presence of some calcification.



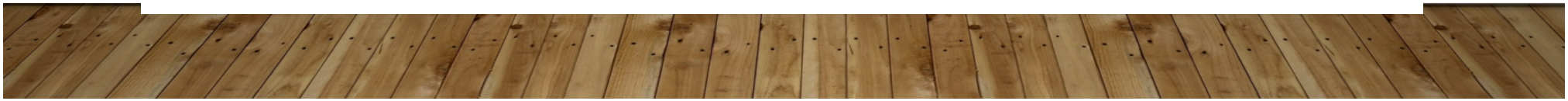


Benign pattern of calcification

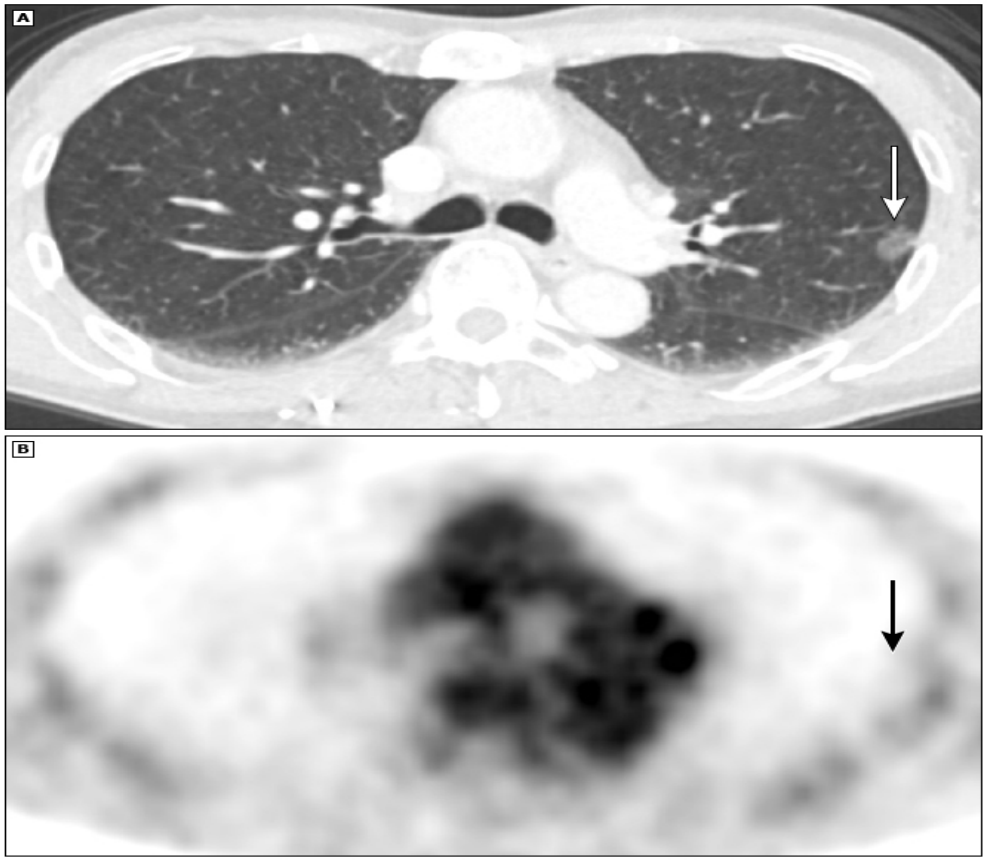
Calcification

Diffuse, central, laminated or popcorn calcifications are benign patterns of calcification.
These types of calcification are seen in granulomatous disease and hamartomas.
All other patterns of calcification should not be regarded as a sign of benignity.

The exception to the rule above is when patients are known to have a primary tumor.
For instance the diffuse calcification pattern can be seen in patients with osteosarcoma or chondrosarcoma.
Similarly the central and popcorn pattern can be seen in patients with GI-tumors and patients who previously had chemotherapy.



CT and FDG PET of a pure ground-glass pulmonary nodule



Pure ground-glass subsolid pulmonary nodule. Chest CT (A) shows a nodule (arrow) of ground-glass density measuring <30 mm in the left upper lobe that on FDG PET (B) demonstrates no tracer avidity (arrow). Pathology showed adenocarcinoma.

CT: computed tomography; FDG: fluorodeoxyglucose; PET: positron emission tomography.

Courtesy of Shaunagh McDermott, MD.

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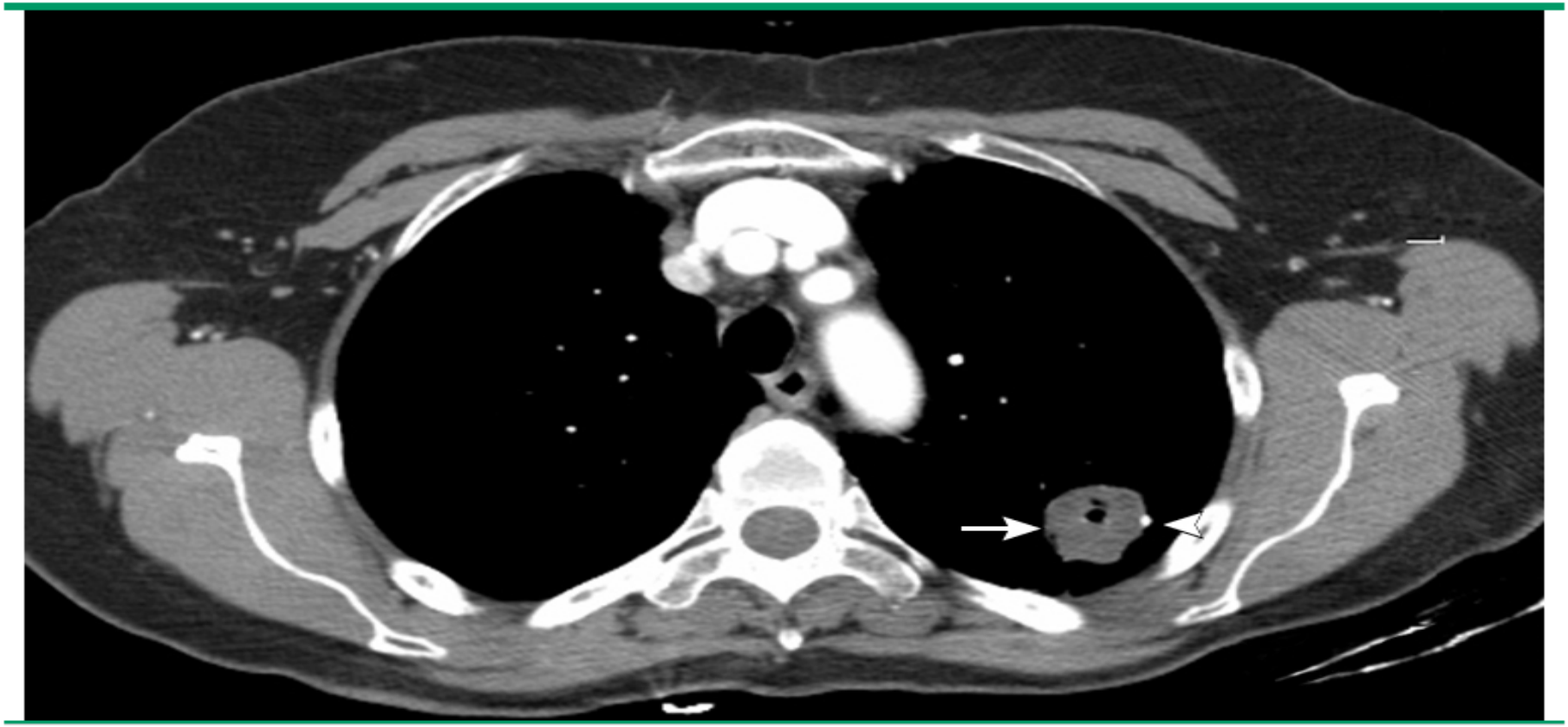
CT of a cavitating atypical mycobacterium pulmonary nodule



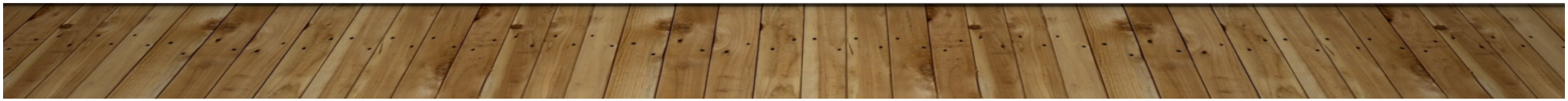
Atypical mycobacterium. Chest CT with contrast shows a 2.8 cm nodule (arrow) and punctate calcification (arrowhead). Central lucency within the nodule indicates cavitation.

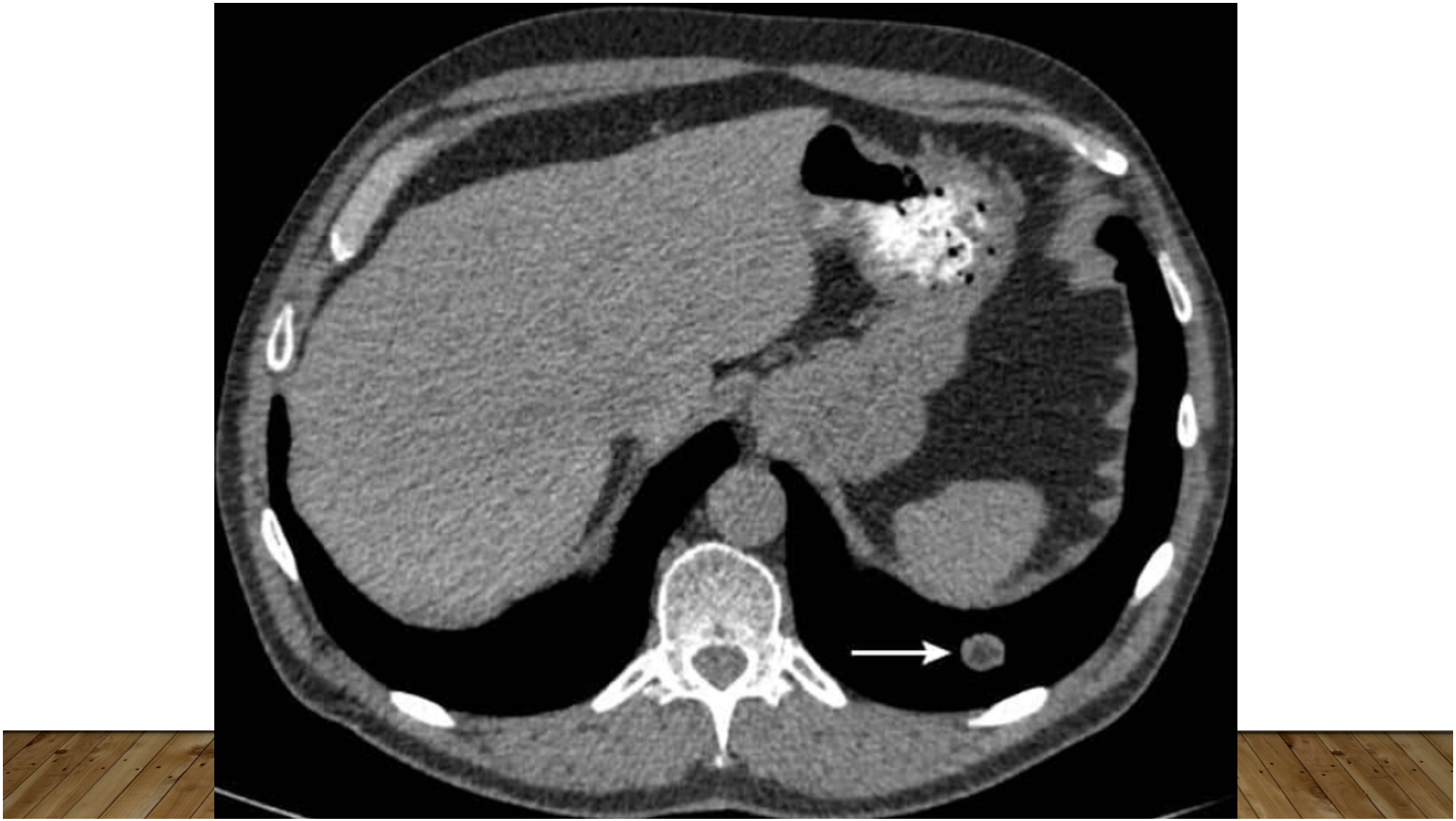
CT: computed tomography.

- Indeterminate patterns of calcification (eg, punctate, eccentric, and amorphous) are nonspecific and a nodule containing one of these patterns may be malignant

- Metastases from chondrosarcoma or osteosarcomas, in patients who carry a diagnosis of these cancers, may demonstrate calcified nodules that resemble benign granulomas.

- The presence of fat (attenuation, -40 to -120 HU) within a smooth bordered nodule is a reliable indicator of a pulmonary hamartoma



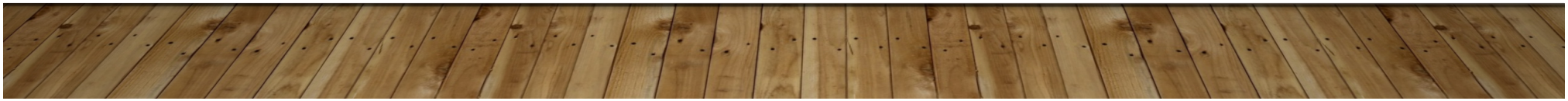


BORDER AND LOBAR LOCATION

- Typically, benign nodules have a well-defined, smooth border, whereas malignant lesions have a speculated or lobular border. Speculation is attributed to growth of malignant cells along the pulmonary interstitium, and lobulation to differential growth rates within nodules.

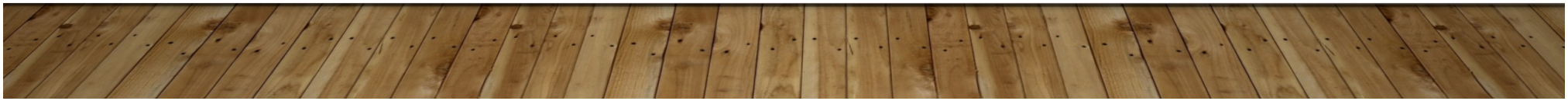
- While the majority of lesions with a speculated margin (also described as a corona radiata sign) are malignant, this can also be seen with benign lesions.

- Conversely, a smooth margin does not exclude malignancy with many pulmonary metastases, and up to 20 percent of lung cancers have smooth margins



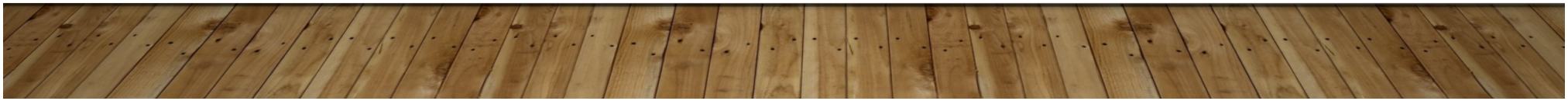
- Although malignant nodules can be found in any lobe of the lung, those that are located in the upper lobe have an increased probability of being malignant

- In addition, among the 77 perifissural nodules observed on CT, none were reported as malignant



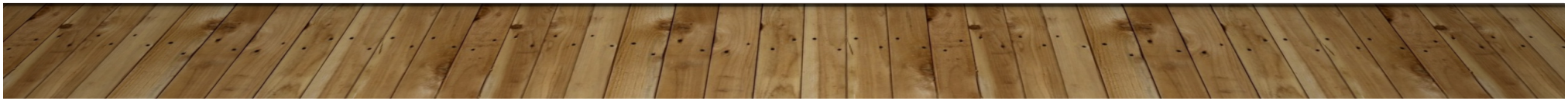
ENHANCEMENT

- Enhancement is calculated by subtracting the precontrast attenuation of the nodule from the peak attenuation after contrast. Typically, malignant nodules enhance more than 20 HU, whereas nodules that enhance <15 HU are likely benign

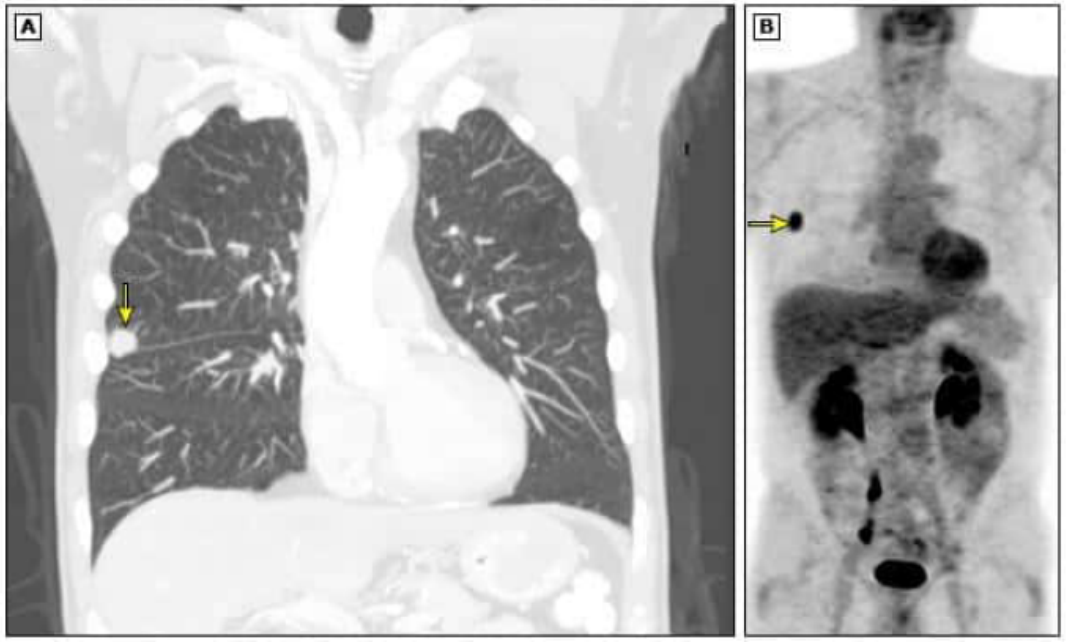


POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY

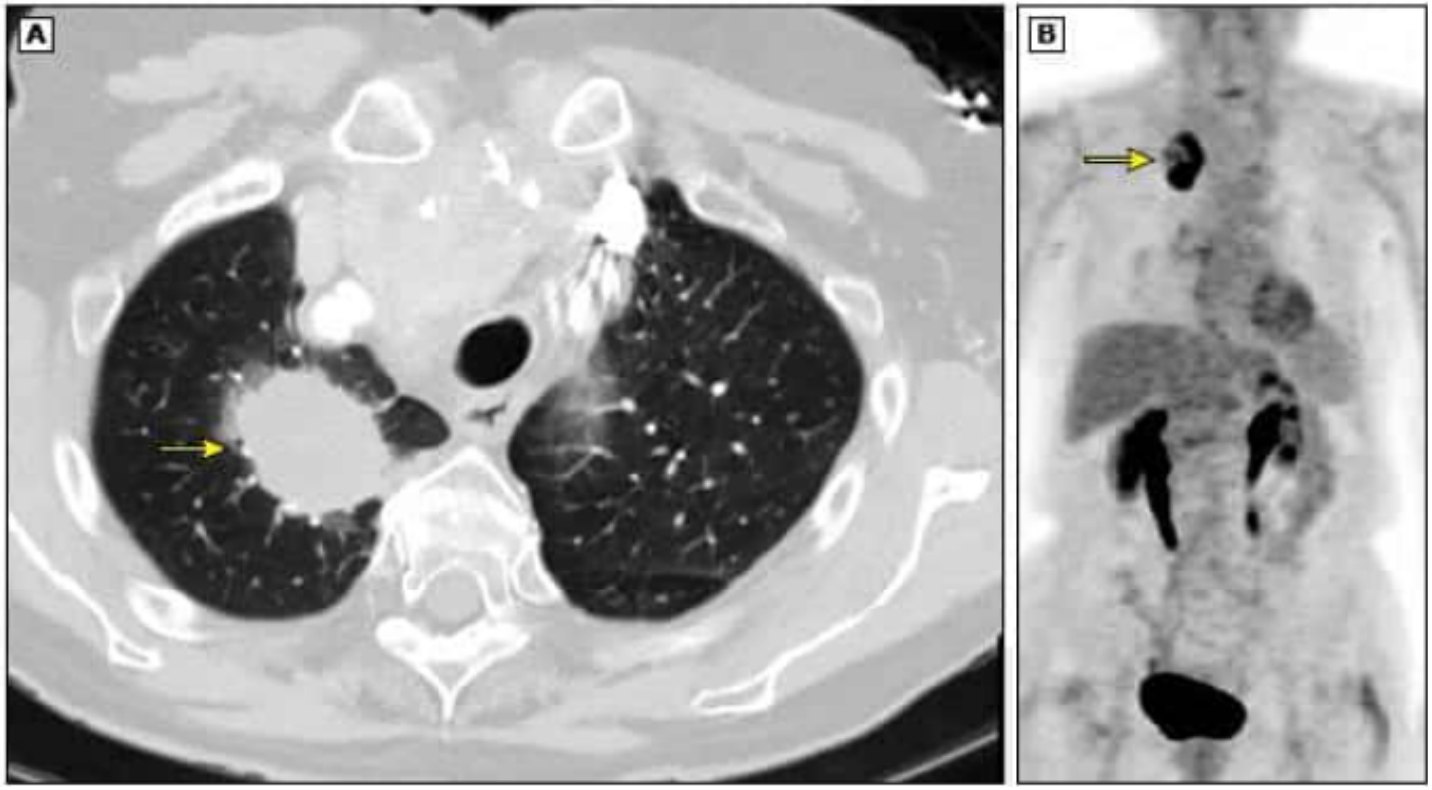
- Solid nodules measuring >8 mm that are not FDG-avid are likely to be benign
- As inflammation and infection are also FDG-avid, specificity is lower by 16 percent in populations with endemic infectious lung disease
- In contrast to solid nodules, ground-glass nodules, or ground-glass portions of part-solid nodules, are not reliably characterized with PET



T1bN0M0 non-small cell lung cancer on CT and PET scans



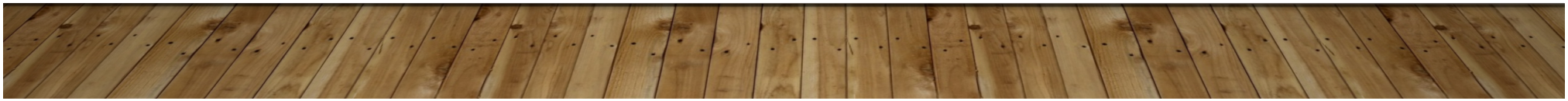
Stage IIA non-small cell lung cancer on CT and PET



FDG PET CAN YIELD FALSE-POSITIVE AND FALSE-NEGATIVE FINDINGS:

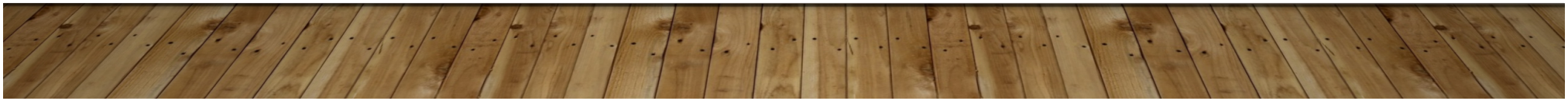
- False-positive findings occur with infectious and inflammatory conditions, in particular, pneumonia, mycobacterial disease, rheumatoid nodules, and sarcoidosis.

- False-negative results can occur with less metabolically active tumors (adenocarcinoma in situ, minimally invasive adenocarcinoma, mucinous adenocarcinoma, and carcinoid tumors) and in patients with uncontrolled hyperglycemia



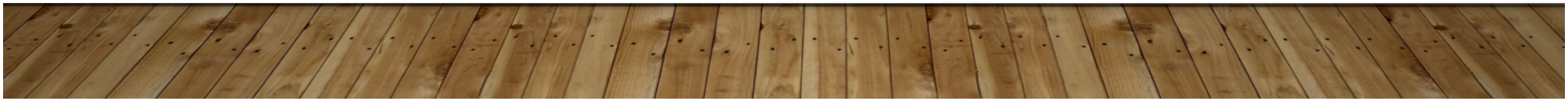
- an SUV >2.5 is typically used to distinguish pulmonary nodules that have a high probability of malignancy

- although SUV correlates positively with the likelihood of malignancy, even nodules with a low SUV (eg, <2.5) can be malignant



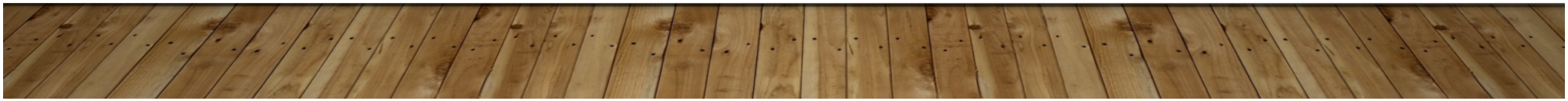
GROWING NODULE

- For solid nodules, growth is defined as an increase in diameter of >2 mm, rounded to the nearest millimeter [65]. For subsolid nodules, growth can also be identified as an increased attenuation or an increase in the size of or development of a solid component



STABLE NODULE

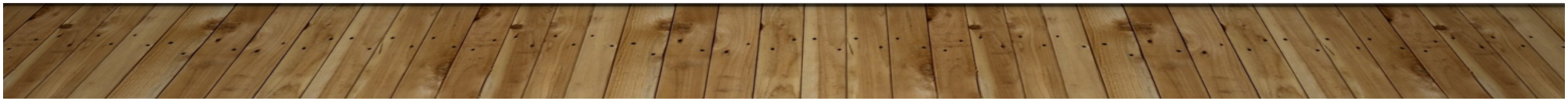
- A solid nodule that has been stable for ≥24 months and a subsolid nodule that is stable for ≥5 years by CT are likely to be benign, and further workup can be avoided.



INDETERMINATE NODULE

- If a nodule cannot be characterized as benign or as requiring tissue diagnosis and has been detected on a CT which incompletely images the chest (eg, neck, abdomen, or spine CT), a dedicated chest CT without contrast should be obtained with a volumetric thin-section scanning protocol.

- If the chest CT demonstrates additional findings relevant to the diagnosis (eg, other nodules or mass, lymphadenopathy, consolidation), further workup should be redirected accordingly



Evaluation of the incidental solid pulmonary nodule in adults

Nodule size (mm)	Low (<5%) cancer risk	High (>65%) or moderate (5 to 65%) cancer risk
Solitary		
<6	No routine follow-up	Optional CT at 12 months
6 to 8	CT at 6 to 12 months, then consider CT at 18 to 24 months	CT at 6 to 12 months, then CT at 18 to 24 months
>8	CT at 3 months, then at 9 and 24 months	FDG PET/CT, biopsy or resection
Multiple (evaluation based on largest nodule)		
<6	No routine follow-up	Optional CT at 12 months
≥6	CT at 3 to 6 months, then consider CT at 18 to 24 months	CT at 3 to 6 months, then CT at 18 to 24 months

1. Not applicable to patients age <35 years, in lung cancer screening, with immunosuppression, known pulmonary disease or symptoms or active primary cancer.
2. Chest CT performed without contrast as contiguous 1 mm sections using low dose technique.
3. Growing or FDG-avid nodules should undergo biopsy or resection. Growth is defined as >1.5 mm increase.
4. Nodules unchanged for >2 years are benign.

CT: computed tomography; FDG: 18-fluorodeoxyglucose; PET: positron emission tomography.

Adapted with permission from: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT Images: From the Fleischner Society. Radiology 2017; 284:228. Copyright © 2017 Radiological Society of North America.

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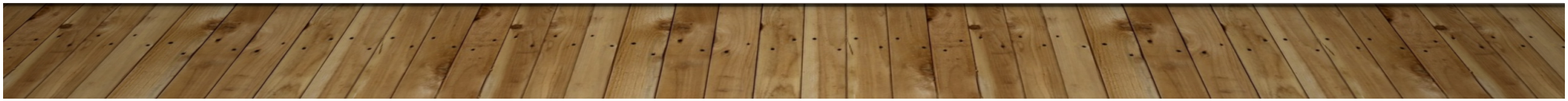


GOALS OF INITIAL EVALUATION

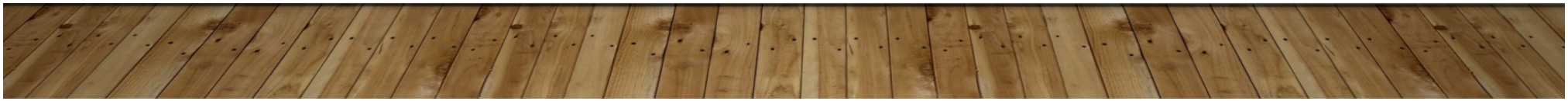
- Clinical extent and stage of disease
- Optimal target site and modality for tissue biopsy
- Specific histologic subtype and genotype of the cancer
- Presence of comorbidities, secondary complications, and paraneoplastic syndromes that influence treatment options and outcome
- Patient values and preferences that influence diagnostic and therapeutic choices

When feasible, our goal is to establish diagnosis and staging concurrently by targeting a lesion or site that establishes the most advanced stage (eg, thoracentesis with cytology examination of fluid to establish stage IV disease).

TIMING

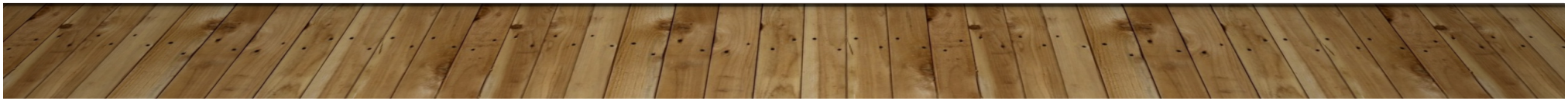
- For patients who have a delay in completion of evaluation by eight weeks or more from the time of initial imaging, we reimage to evaluate a change in stage since some cases are rapidly growing and can progress during the evaluation period.

- One case series reported disease progression in 13 percent of patients at four weeks, 31 percent at eight weeks, and 46 percent at 16 weeks, respectively, with distant metastasis newly evident in 3, 13, and 13 percent of cases



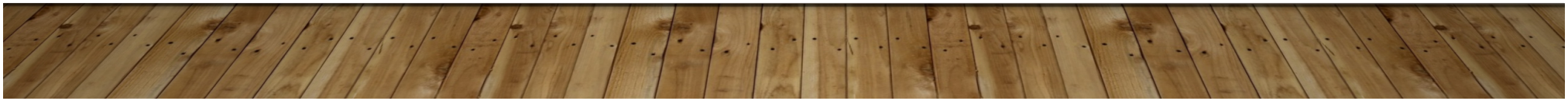
- Location: outpatient , some needs admission
- Patient values and preferences

- In patients with suspected lung cancer, we review all current chest imaging and compare with prior imaging, since the time course of identified lesions is an important determinant of the likelihood that a nodule or mass represents cancer



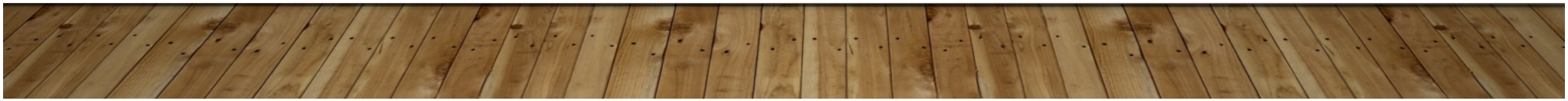
THE FOLLOWING IMAGING FEATURES SHOULD RAISE THE SUSPICION FOR LUNG CANCER

- Lesions larger than 3 cm that are new
- Measurable growth in any nodule or mass
- Pleural nodularity
- Asymmetric or significantly enlarged hilar or paratracheal nodes
- An endobronchial lesion
- An area of consolidation thought to be pneumonia that fails to resolve with medical management



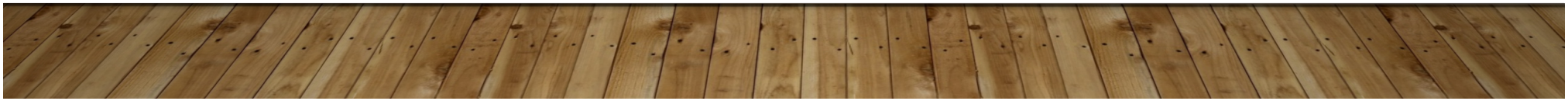
CONCERNING BUT LESS SPECIFIC

- Pleural effusions
- Non-dependent or substantial atelectasis
- Pleural plaques may indicate significant asbestos exposure



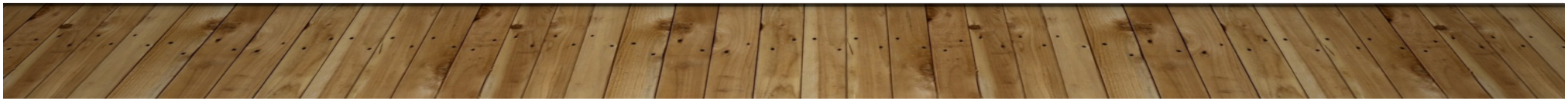
ADDITIONAL FEATURES ON CHEST CT SUGGESTIVE OF MALIGNANCY

- Lesions with an irregular or speculated border
- Thick-walled cavitary lesions (especially in the absence of findings for active infection)
- Nodules with mixed attenuation, containing a solid component and a less dense ground-glass component
- Pure ground-glass lesions, when persistent or slowly increasing in size over months to years (can be atypical adenomatous hyperplasia, carcinoma in situ, or minimally invasive or frankly invasive adenocarcinoma)
- Multiple nodules (may suggest metastases, though a dominant nodule or mass with additional nodules may be a lung cancer with concurrent benign nodules or metastases)



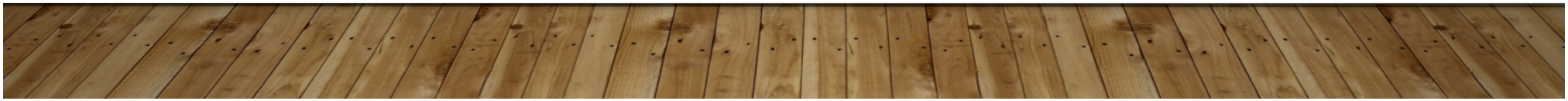
- Every patient with suspected lung cancer should have contrast-enhanced chest computed tomography (CT).

- Chest CT is generally best performed as a stand-alone test even if whole-body positron emission tomography (PET)/CT is obtained, since PET/CT studies often are done without contrast and with lower-resolution CT images



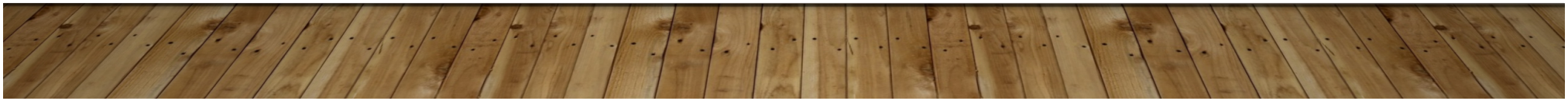
COMPREHENSIVE IMAGING FOR POTENTIAL SITES OF METASTASES

- This approach uses chest CT and the selective use of whole-body F -fluorodeoxyglucose PET/CT (FDG PET/CT) with or without brain MRI to determine the highest likely radiologic stage and optimal biopsy site.



PET HAS SEVERAL LIMITATIONS:

- False positives can occur with benign FDG-avid lesions such as infections, inflammation, and granulomatous disease (approximately 10 to 30 percent, depending on the population)
- Conversely, false-negatives typically occur in the setting of microscopic foci of metastasis, and in nonenlarged lymph nodes (eg, <10 mm)

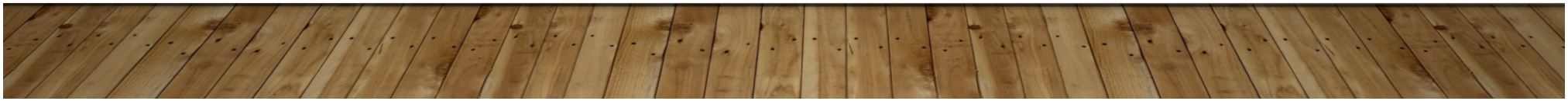


PANELS OF IHC STAINS

- Adenocarcinoma is typically positive for thyroid transcription factor (TTF-1), mucin, napsin-A, surf-A, surf-B, PAS-D, and cytokeratin (CK) 7

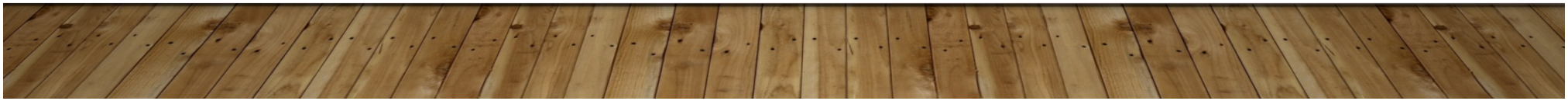
- Squamous cell carcinoma is typically positive for p40, p63, and CK 5/6, and usually negative for CK 7

- SCLC can be positive for TTF-1. However, as a neuroendocrine tumor, SCLC should have no other shared IHC staining patterns with NSCLC and is typically positive for synaptophysin, CD 56, chromogranin, or neuron-specific enolase, while NSCLC is negative for these stains.



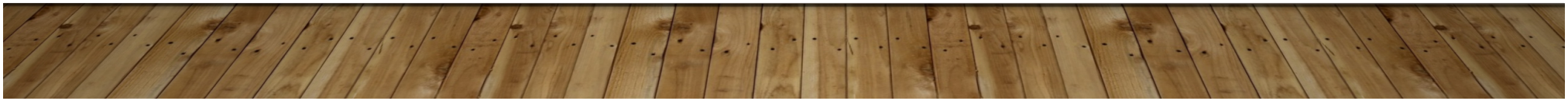
- Poorly differentiated cancers and metastases from distant sites may need to be distinguished from primary NSCLC.

- As examples, stains that are classically negative in NSCLC are CK 20 (typically positive in adenocarcinoma of the colon) and estrogen and progesterone receptor (typically positive in adenocarcinoma of the breast), thereby distinguishing the tissue of origin for adenocarcinoma found in the lung



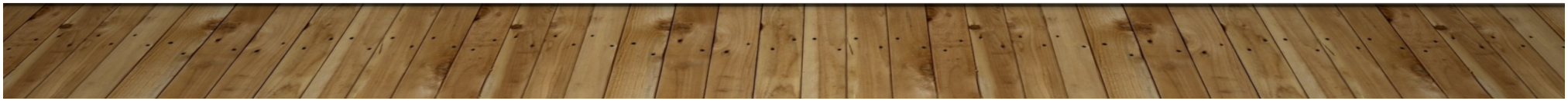
THE COMMON GENETIC MUTATIONS

- epithelial growth factor receptor gene (EGFR), rearrangements of the anaplastic lymphoma kinase gene (ALK)
- NSCLC samples are also typically tested for anti-programmed cell death ligand 1 expression for suitability for immune checkpoint inhibitor therapy



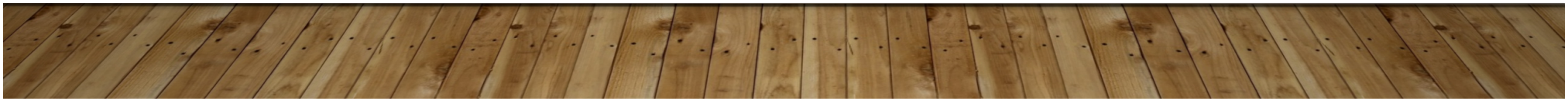
SUPERIOR VENA CAVA SYNDROME

- The three most common malignancies associated with SVC syndrome are NSCLC, SCLC, and lymphoma



PARANEOPLASTIC PHENOMENA

- Paraneoplastic effects of tumor are remote effects that are not related to the direct invasion, obstruction, or metastasis

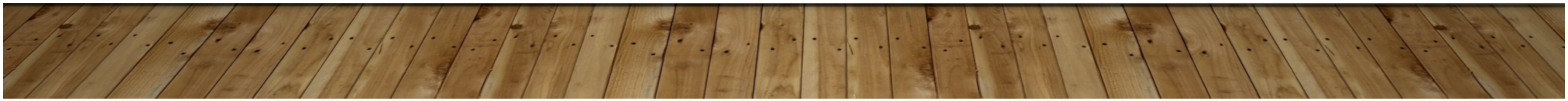


HYPERCALCEMIA

- Hypercalcemia in patients with lung cancer may arise from tumor secretion of parathyroid hormone-related protein, or less commonly from extensive bony metastases or primary hyperparathyroidism

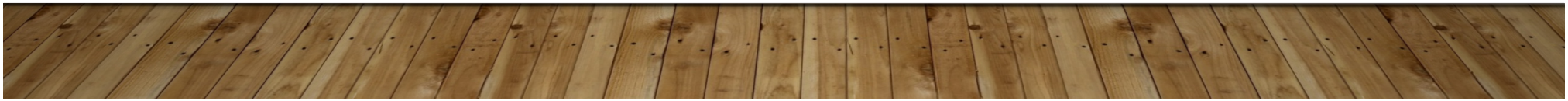
- Symptoms of hypercalcemia include anorexia, nausea, vomiting, constipation, lethargy, polyuria, polydipsia, and dehydration. Confusion and coma are late manifestations as are renal failure and nephrocalcinosis.

- Among those with hypercalcemia, squamous cell carcinoma, adenocarcinoma, and SCLC were responsible in 51, 22, and 15 percent of cases, respectively



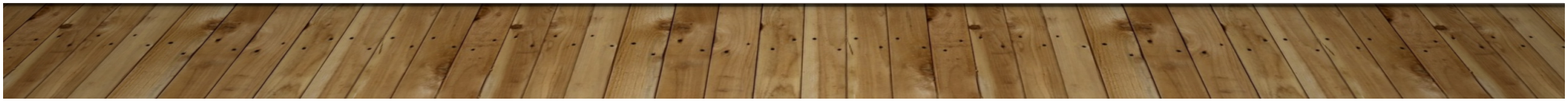
SIADH SECRETION

- The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is frequently caused by SCLC and results in hyponatremia. Approximately 10 percent of patients who have SCLC exhibit SIADH



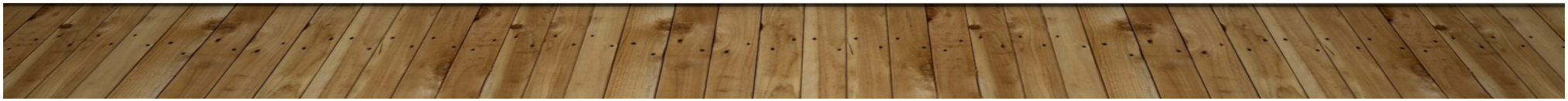
NEUROLOGIC SYNDROMES

- Lung cancer is the most common cancer associated with paraneoplastic neurologic syndromes; typically, these are associated with SCLC
- These diverse neurologic manifestations include, but are not limited to, Lambert-Eaton myasthenic syndrome (LEMS), cerebellar ataxia, sensory neuropathy, limbic encephalitis, encephalomyelitis, autonomic neuropathy, retinopathy, and opsomyoclonus



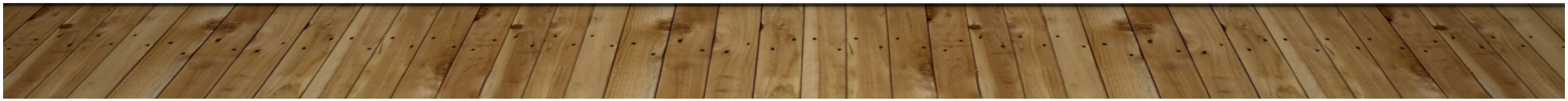
- As many as 70 percent of patients who have SCLC and an associated paraneoplastic neurologic syndrome have limited-stage disease .

- The finding of a paraneoplastic autoantibody in patients presenting with a neurologic syndrome should lead to an evaluation for malignancy.



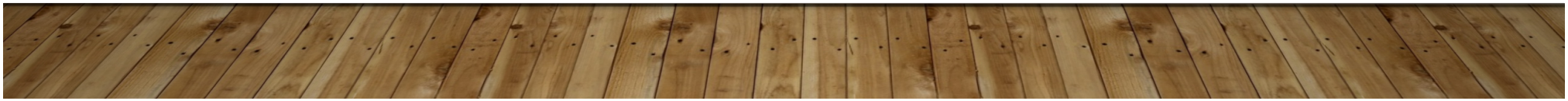
HEMATOLOGIC MANIFESTATIONS

- Anemia
- Leukocytosis
- Thrombocytosis
- Eosinophilia
- Hypercoagulable disorders



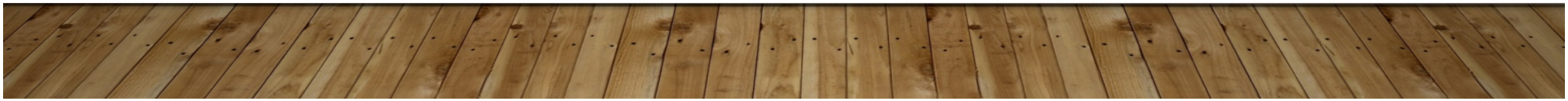
HYPERTROPHIC OSTEOARTHROPATHY

- HPO is characterized by a symmetrical, painful arthropathy and long-bone pain that usually involves the ankles, knees, wrists, and elbows
- The symptoms of HPO may resolve after tumor resection



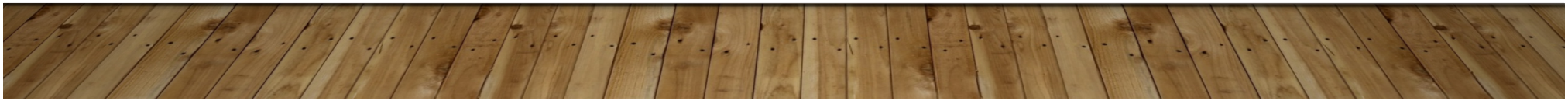
DERMATOMYOSITIS AND POLYMYOSITIS

- Dermatomyositis and polymyositis are two distinct forms of inflammatory myopathy, both of which are manifested clinically by muscle weakness.
- These inflammatory myopathies can be the presenting symptom in patients with lung cancer or can develop later in the course of disease.
- In addition to lung cancer, other frequent primary sites associated with these disorders include the ovary, cervix, pancreas, bladder, and stomach.

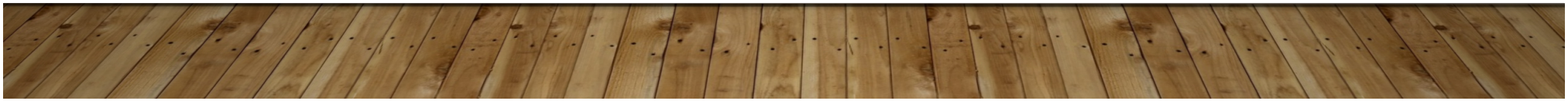


CUSHING SYNDROME

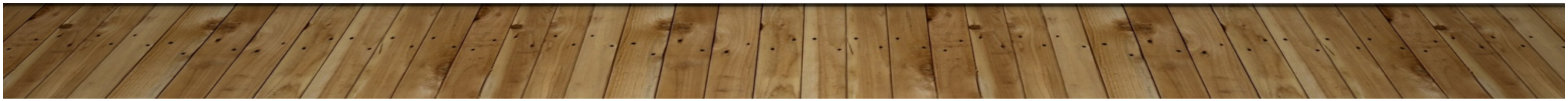
- Ectopic production of adrenal corticotropin can cause Cushing syndrome. Patients typically present with muscle weakness, weight gain, hypertension, hirsutism, and osteoporosis.
- However, when Cushing syndrome is due to SCLC, weight loss is more often present . Hypokalemic alkalosis and hyperglycemia are usually present
- Cushing syndrome is rare, but is most seen in patients with SCLC, large cell neuroendocrine carcinoma, or carcinoid tumors of the lung



T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor â‰¤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)*
T1a(mi)	**Minimally invasive adenocarcinoma**ÂÂ¶
T1a	**Tumor â‰¤1 cm in greatest dimension***
T1b	**Tumor >1 cm but â‰¤2 cm in greatest dimension***
T1c	**Tumor >2 cm but â‰¤3 cm in greatest dimension***
T2	Tumor >3 cm **but â‰¤5 cm** or tumor with any of the following features:[†] ■ **Involves main bronchus regardless of distance from the carina but without involvement of the carina** ■ Invades visceral pleura ■ **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**
T2a	**Tumor >3 cm but â‰¤4 cm in greatest dimension**
T2b	**Tumor >4 cm but â‰¤5 cm in greatest dimension**
T3	**Tumor >5 cm but â‰¤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm**, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina



N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[å–Š]
M1b	**Single extrathoracic metastasis**[åß]
M1c	**Multiple extrathoracic metastases in one or more organs**



Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	**T1a(mi)**	**N0**	**M0**
	T1a	**N0**	**M0**
Stage IA2	**T1b**	**N0**	**M0**
Stage IA3	**T1c**	**N0**	**M0**
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	**T1a to c**	**N1**	**M0**
	T2a	**N1**	**M0**
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	**T1a to c**	**N2**	**M0**
	T2a to b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	**T1a to c**	**N3**	**M0**
	T2a to b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**
Stage IVA	**Any T**	**Any N**	**M1a**
	Any T	**Any N**	**M1b**
Stage IVB	**Any T**	**Any N**	**M1c**