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# Optimal follow-up of incidental nodules

W De Wever

University Hospitals - Dept of Radiology - Leuven, Belgium

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EUROPEAN LUNG CANCER  
CONFERENCE

Geneva, Switzerland  
**15-18 APRIL 2015**



# Optimal follow-up of incidental nodules

- No conflict of interests



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# Optimal follow-up of incidental nodules

- Definition of incidental nodules
- Management strategies for follow-up of incidental nodules
  - Pretest probability of malignancy
  - Characterisation of nodules

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# Definition of nodule

- A **pulmonary nodule** is defined as a focal pulmonary lesion or opacity, round or oval in shape, which measures less than 3 cm in diameter
- Today...
  - focal area of ground glass attenuation and all small opacities only a few millimeters in size discovered incidentally on CT

# Definition of incidental nodule

- **Incidental nodule:** nodule detected incidentally during the course of CT performed for other reasons than lung cancer screening
  - < 1% of very small (<5mm) nodules in patients without a history of cancer will demonstrate malignant behavior
- **Indeterminate nodule:** nodule that is not calcified in a benign pattern and that has not been shown to be stable after > 2 years of follow-up

# Frequency of incidental pulmonary nodules

- Detection of pulmonary nodules with chest CT increases:
  - with the **increasing use** of CT technology
  - with the **evolution** of CT technology
    - conventional CT vs spiral CT vs MDCT
    - superior spatial and contrast resolution

# Frequency of incidental pulmonary nodules

Author	Year	Reason of examination	Slice thickness on CT	Detection rate of pulmonary nodules
Chalmers et al. <i>Clin Radiol</i> 1991; 44(6):410-2	1991	Extrapulmonary malignant neoplasms	10 mm	13%
Henschke et al. <i>Lancet</i> 1999,354(9173):99-105	1999	Lung cancer screening	10 mm	23%
Diederich et al. <i>Radiology</i> 2002;222(3):773-81	2002	Asymptomatic former smokers > 40 years	5 mm	43%
Swensen et al. <i>Radiology</i> 2005;235(1):259-65	2005	Smokers > 50 year	3,75 mm	74%
Hanamiya et al. <i>Eur J Radiol</i> 2012;81(1):152-7	2012	Extrapulmonary malignant neoplasms	2 mm	75%



# Frequency of incidental pu

- **Pulmonary nodules**
  - are a common finding on CT in smokers and
  - are frequently multiple
  - are usually smaller than 1 cm in diameter
- **Most of these small nodules**
  - uncertain significance at the time of discovery
  - require further evaluation
- **Result**
  - an increase in workload for radiology departments
  - repeated clinic appointments
  - increase of non-invasive and invasive diagnostic tests
  - Increased anxiety for patients

**Table 1** Causes of incidentally discovered solid pulmonary nodules

## Aetiological classification

Neoplastic	Primary pulmonary carcinoma (adenocarcinoma, bronchioloalveolar carcinoma, squamous cell carcinoma, small cell carcinoma)
Malignant	Primary pulmonary lymphoma Primary pulmonary carcinoid Lung metastasis
Benign	Hamartoma, fibroma, chondroma, leiomyoma, lipoma
Infectious or inflammatory	Granulomas Opportunistic infection Round pneumonia Abscess Focal organising pneumonia Cicatrizing fibrosis Necrobiotic nodule in rheumatoid arthritis Wegener's granulomatosis
Vascular	Pulmonary artery aneurysm Pulmonary varices Pulmonary arteriovenous malformation Pulmonary infarct Haematoma
Miscellaneous	Intrapulmonary lymph node Rounded atelectasis Bronchogenic cyst Mucoid impaction

Beigelman-Aubry C, Eur Radiol 2007; 17:449-466



# Management strategies

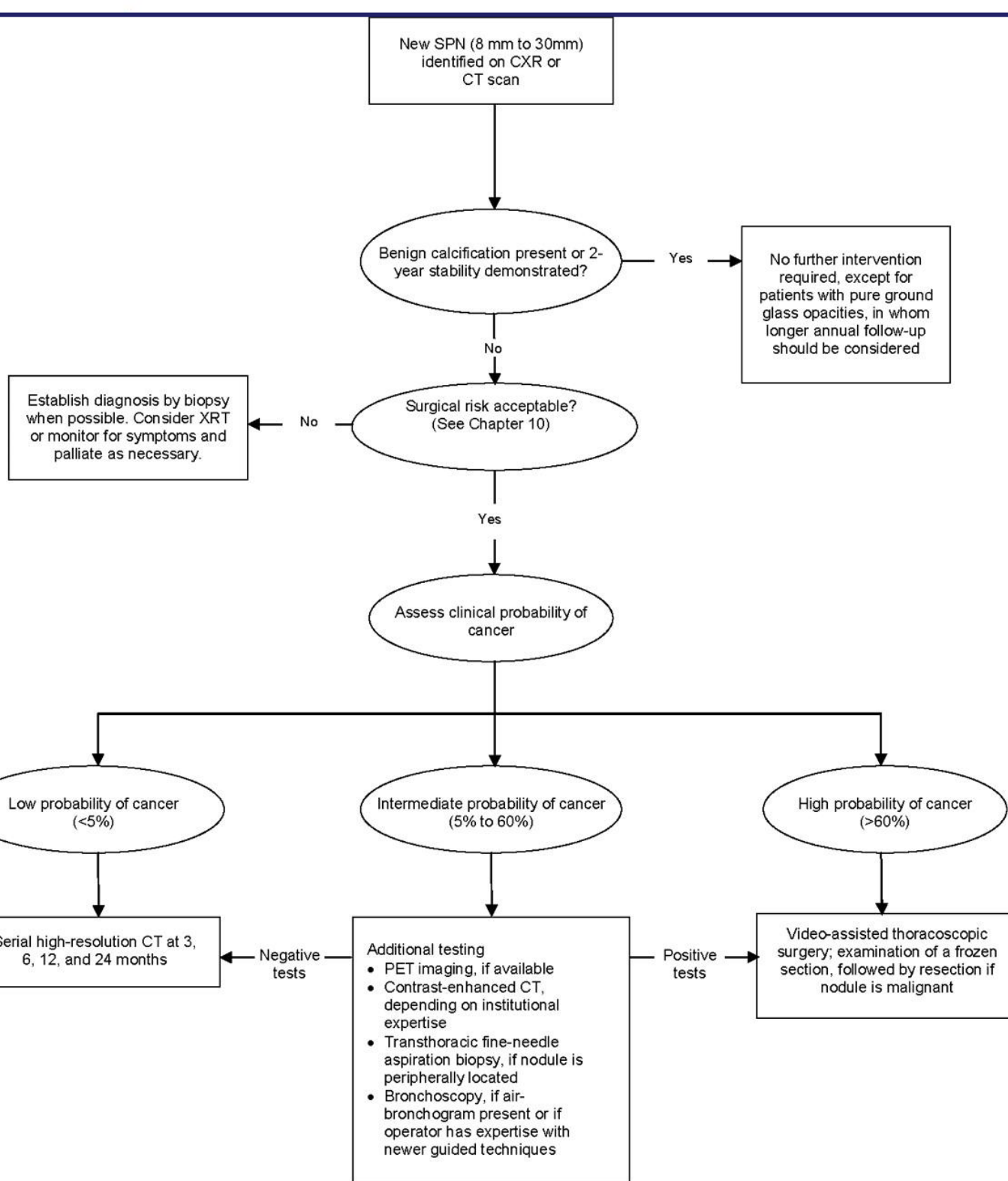
- ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition): 2007

Gould M K et al. Chest 2007;132:108S-130S

- The Fleischner Society's recommendations

MacMahon H et al. Radiology 2005; 237:395-400

Naidich D et al. Radiology 2013; 266(1):304-317



## Pre-test risk

Low risk  
(never smoked and no other risk factors)

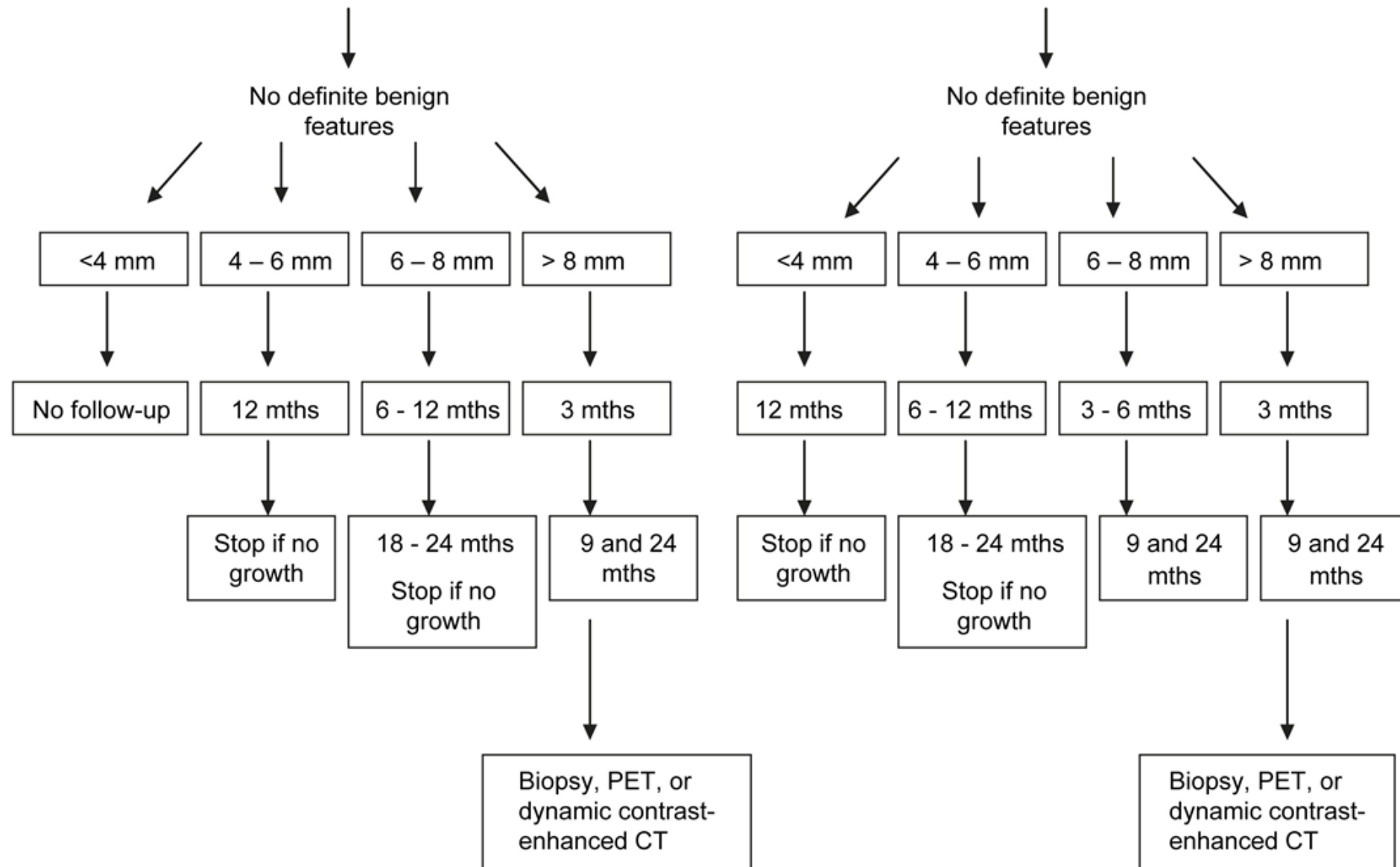
High risk  
(smoker or other risk factors)

## Nodule size

## Initial follow-up

## Subsequent follow-up

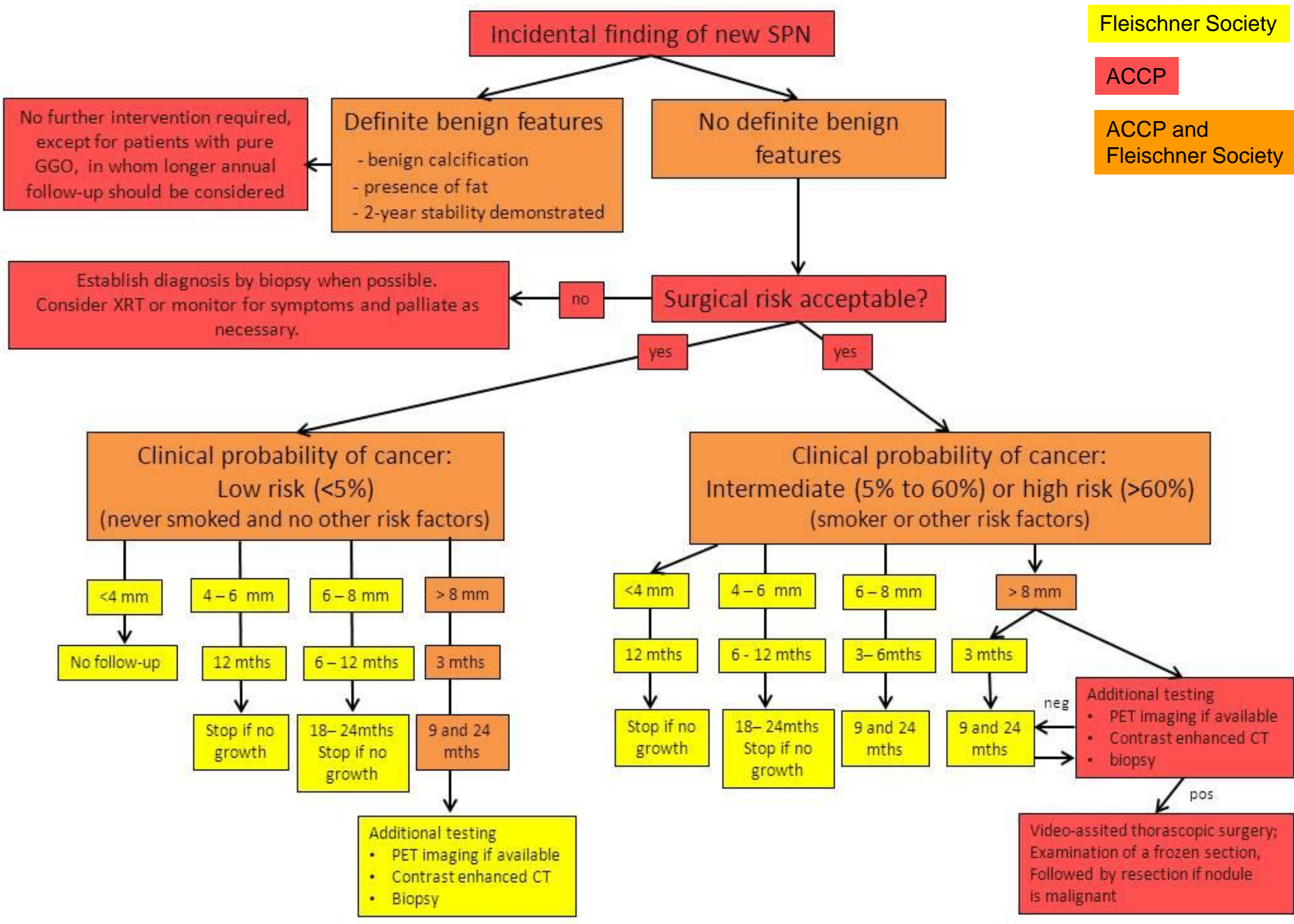
## Additional tests



[Radiology](#). 2005 Nov;237(2):395-400.

**Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society.**

[MacMahon H](#), [Austin JH](#), [Gamsu G](#), [Herold CJ](#), [Jett JR](#), [Naidich DP](#), [Patz EF Jr](#), [Swensen SJ](#); [Fleischner Society](#).



# Management strategies

- **Pretest probability of malignancy**
  - previous history of cancer, patient age, smoking history, nodule size, nodule density
- **Characterisation of nodules**
  - analysis of the density
  - analysis of the morphology
  - analysis of the number of nodules



# Pretest probability of malignancy

The clinical prediction model is described by the following equations:

$$\text{Probability of malignant SPN} = e^x / (1 + e^x)$$

$$X = -8.404 + (2.061 \times \text{smoke}) + (0.779 \times \text{age } 10) + (0.112 \times \text{diameter}) - (0.567 \times \text{years quit } 10)$$

## A Clinical Model To Estimate the Pretest Probability of Lung Cancer in Patients With Solitary Pulmonary Nodules<sup>\*</sup>

**Table 2.**

Predictors of Malignant SPNs

Predictors	OR	95% CI
Smoking history <sup>*</sup>	7.9	2.6-23.6
Age per 10-yr increment	2.2	1.7-2.8
Nodule diameter per 1-mm increment	1.1	1.1-1.2
Time since quitting smoking per 10-yr increment	0.6	0.4-0.7

<sup>\*</sup> Ever vs never.



# Characterisation of nodules

**Table 2** Criteria defining a benign nodule

Benign nodule criteria

Diffuse, dense calcification  
 Vessels converging towards either side of the nodule (pulmonary arteriovenous malformation) or vessels converging towards the pleural side of the nodule/comet-tail sign (rounded atelectasis)  
 Diagnostic criteria of hamartoma (round shape, smooth, regular contours, containing fat density, +/- popcorn calcification)  
 Benign-type calcification (central, target, laminated, concentric)

**Table 3** Criteria defining a nodule as highly suspicious of malignancy (a single criterion is sufficient)

Criteria defining a nodule as highly suspicious of malignancy

Persistent non-solid (focal) ground glass nodule measuring 10 mm or more in diameter  
 Persistent mixed (or part solid) nodules  
 Solid nodule measuring 20 mm or more in diameter  
 Solid nodule with spiculated contours  
 Solid nodule containing air bronchogram or pseudocavitation  
 Solid nodule containing eccentric or dispersed calcifications

**Table 4** Criteria defining an indeterminate nodule

Indeterminate nodule criteria

Persistent ground glass nodule measuring less than 10 mm in diameter  
 Solid nodule of less than 20 mm in diameter with  
     Non-spiculated contours  
     No air bronchogram or pseudocavitation  
     No malignant-type calcification  
     No intralesional fat or benign-type calcification

# Size

Lung cancer screening trials and other	
SPN	Malignant
< 5 mm	< 1%
5 – 10 mm	6 – 28%
10 – 20 mm	41 – 64%
20 – 30 mm	67 – 82%

**Key point:** Size is never a definitive criterion for malignancy, but remains an excellent indicator of the probability of nodule malignancy

# Density

- Rate of malignancy
  - Solid: 7-15%
  - Pure ground glass: 18-34%
  - Part-solid (mixed): 40-63%

**Key point:** The malignancy rate of pure ground-glass nodules and part-solid nodules is higher than that of solid nodules

Wormanns et al., Eur Radiol 2004  
Winer-Muram, Radiology 2006  
Libby, Chest 2004  
Van't Westeinde, Lung Cancer 2008  
Feng, Radiology 2004

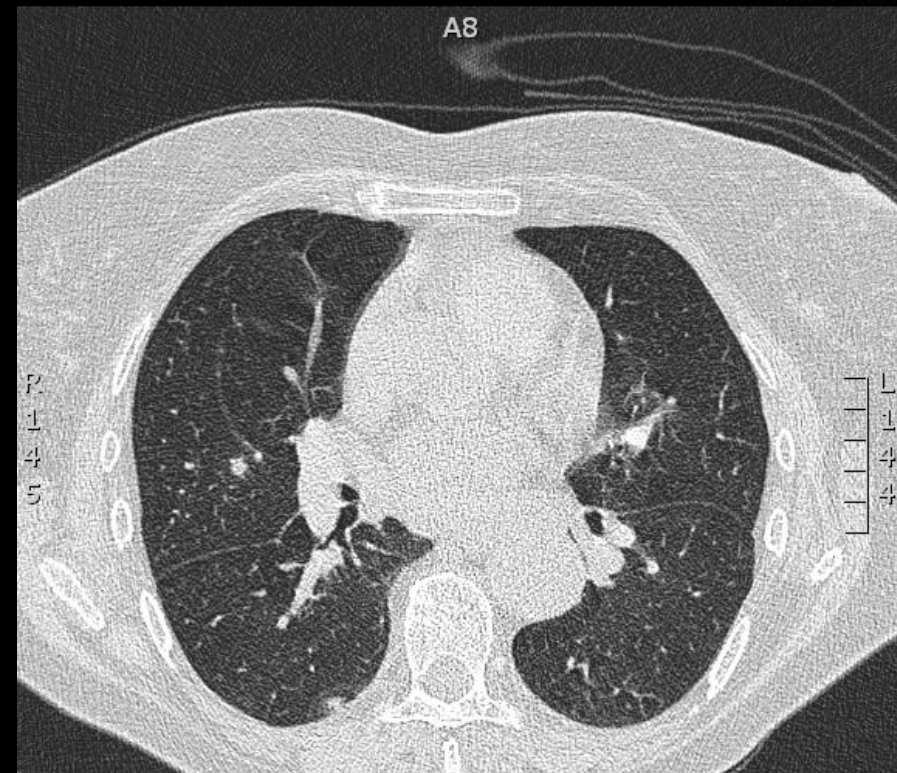
# Density

- **GGO or mixed nodules** (single or multiple) – treatment
  - **Disappeared after 1 month**: inflammatory or infectious lesions
  - **Persisting after 1 month**: a persistent or chronic non-solid nodule
    - **Non-neoplastic**
      - foci of desquamative interstitial pneumonia in a smoker
      - pulmonary fibrosis
      - organising pneumonia
    - **Neoplastic**
      - benign: atypical adenomatous hyperplasia
      - malignant, non-invasive or minimally invasive cancers



18848161 SE:4  
Sensation 16 IM:473  
Sensation16 Z12 11-01-2011  
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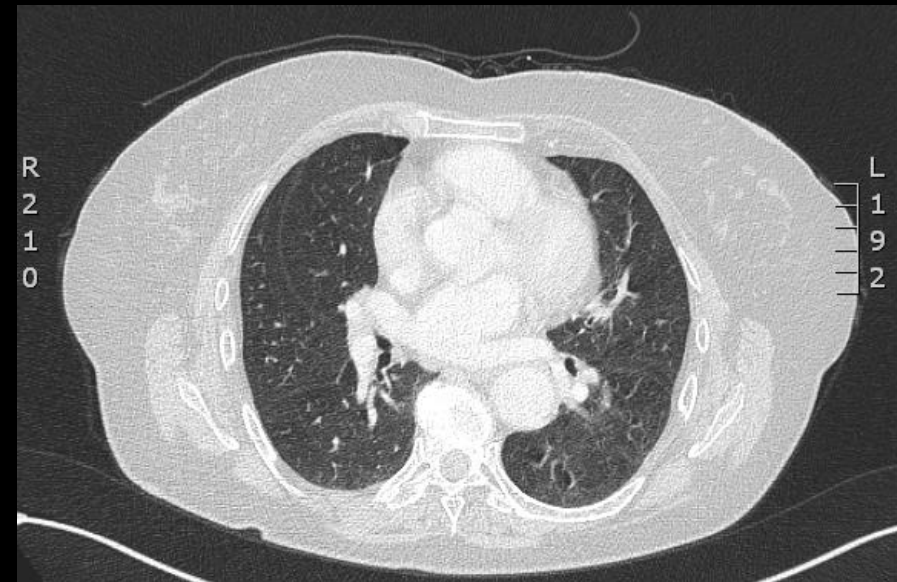


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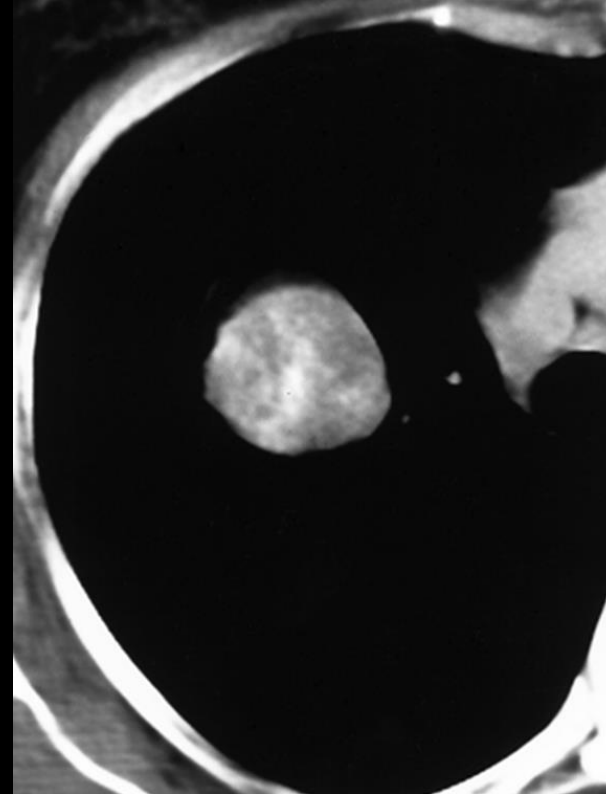
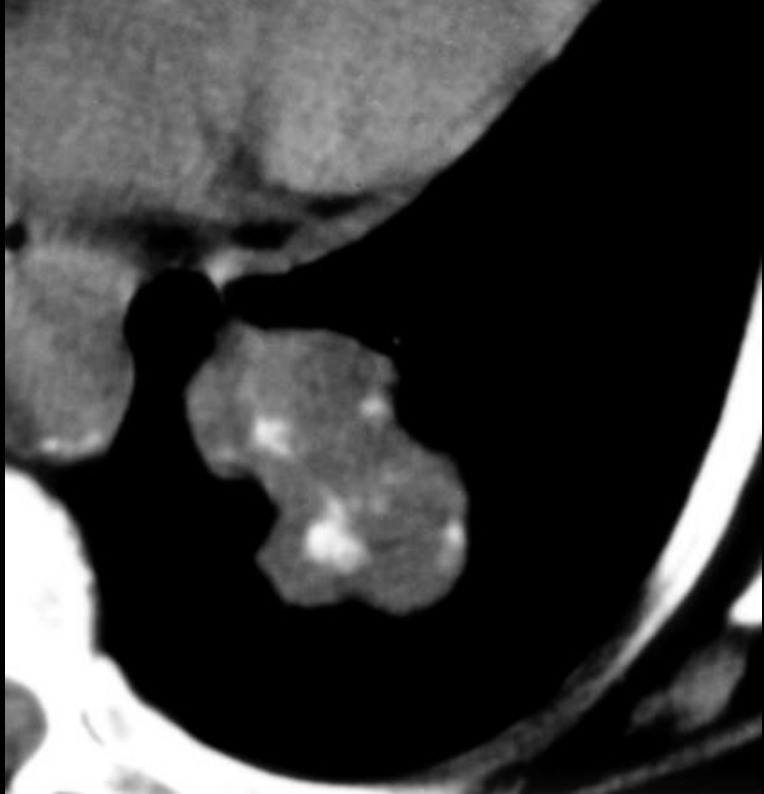
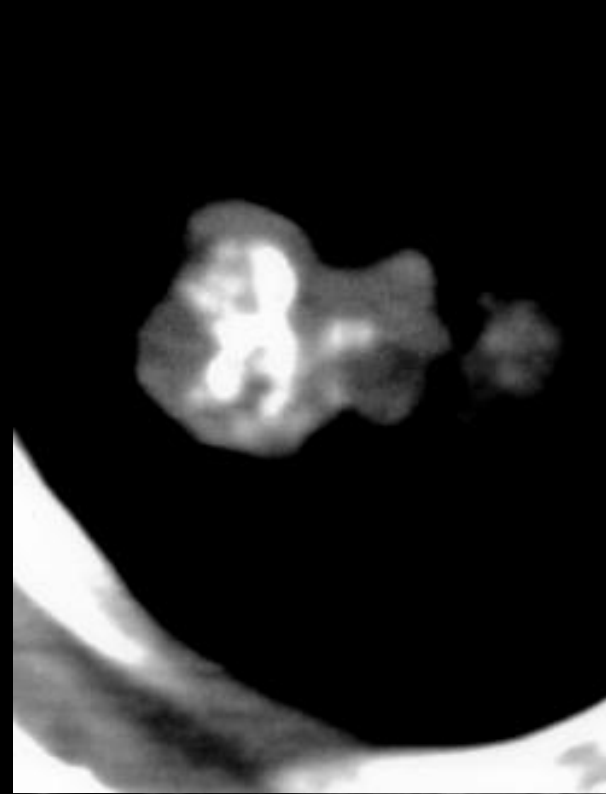
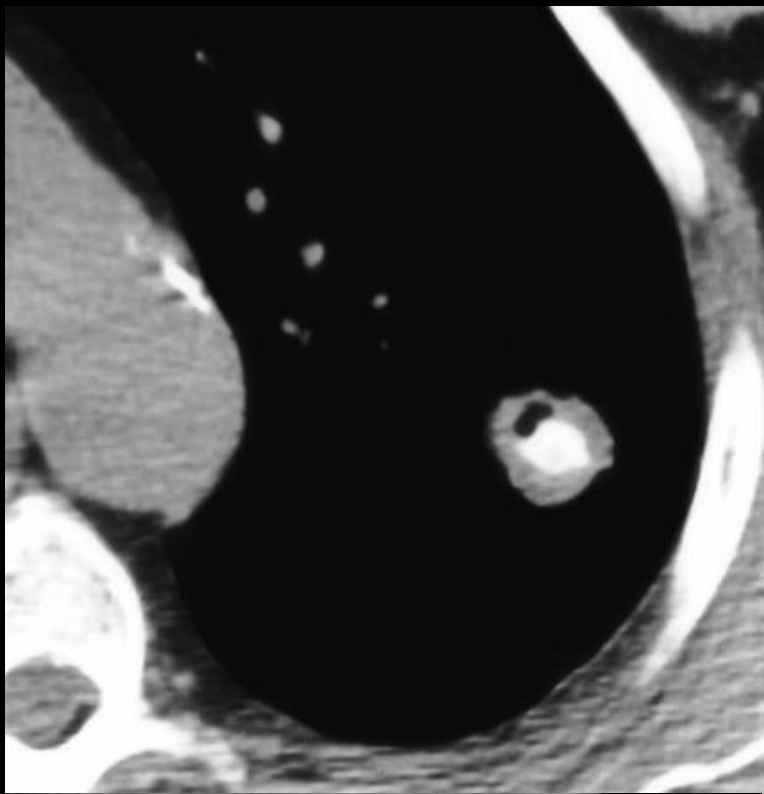
# Calcification

- Benign
  - central
  - laminated
  - diffuse
  - popcorn
- Indeterminate
  - excentric
  - stippled

**Key point:** A benign pattern of calcification is a reliable indicator for a benign lesion

- Exception: metastases from osteosarcoma, chondrosarcoma or synovial sarcoma



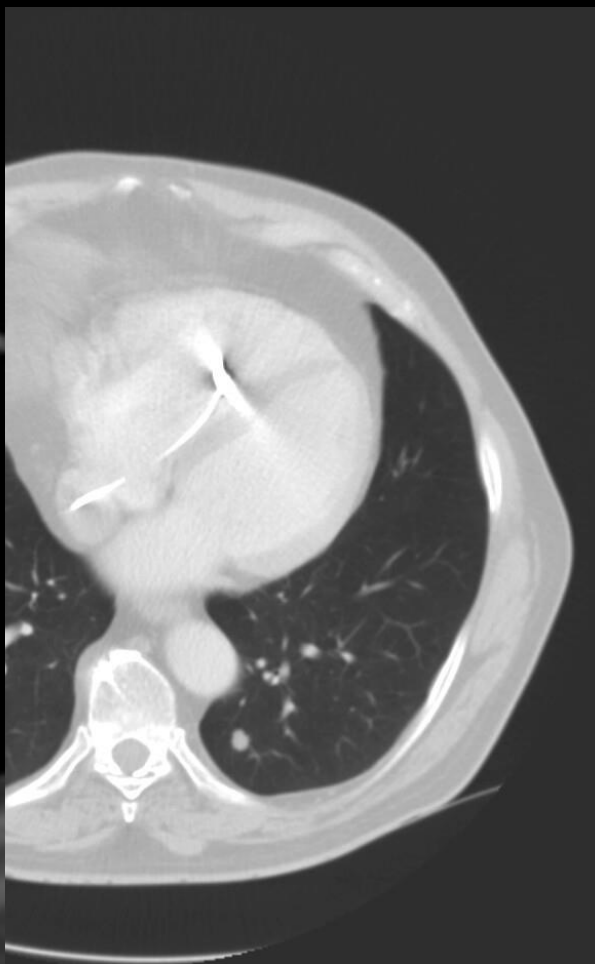
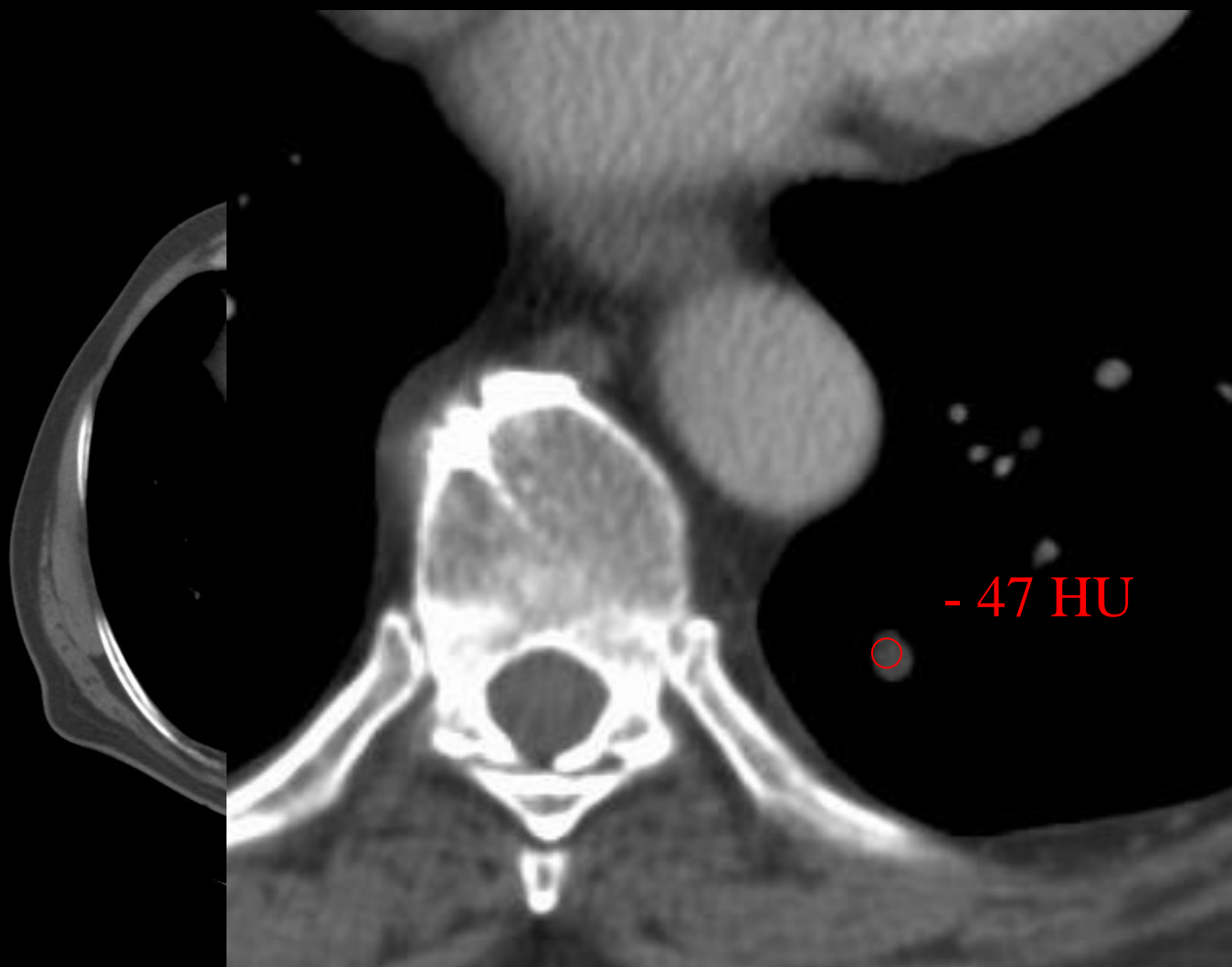


# Fat

- Presence of focal fat in an SPN if HU measurements are between -40 and -120
- SPN with focal fat can be confidently diagnosed as hamartoma or, less likely, lipoidgranuloma or lipoma

**Key point:** Focal fat within a nodule is a reliable indicator for a benign lesion

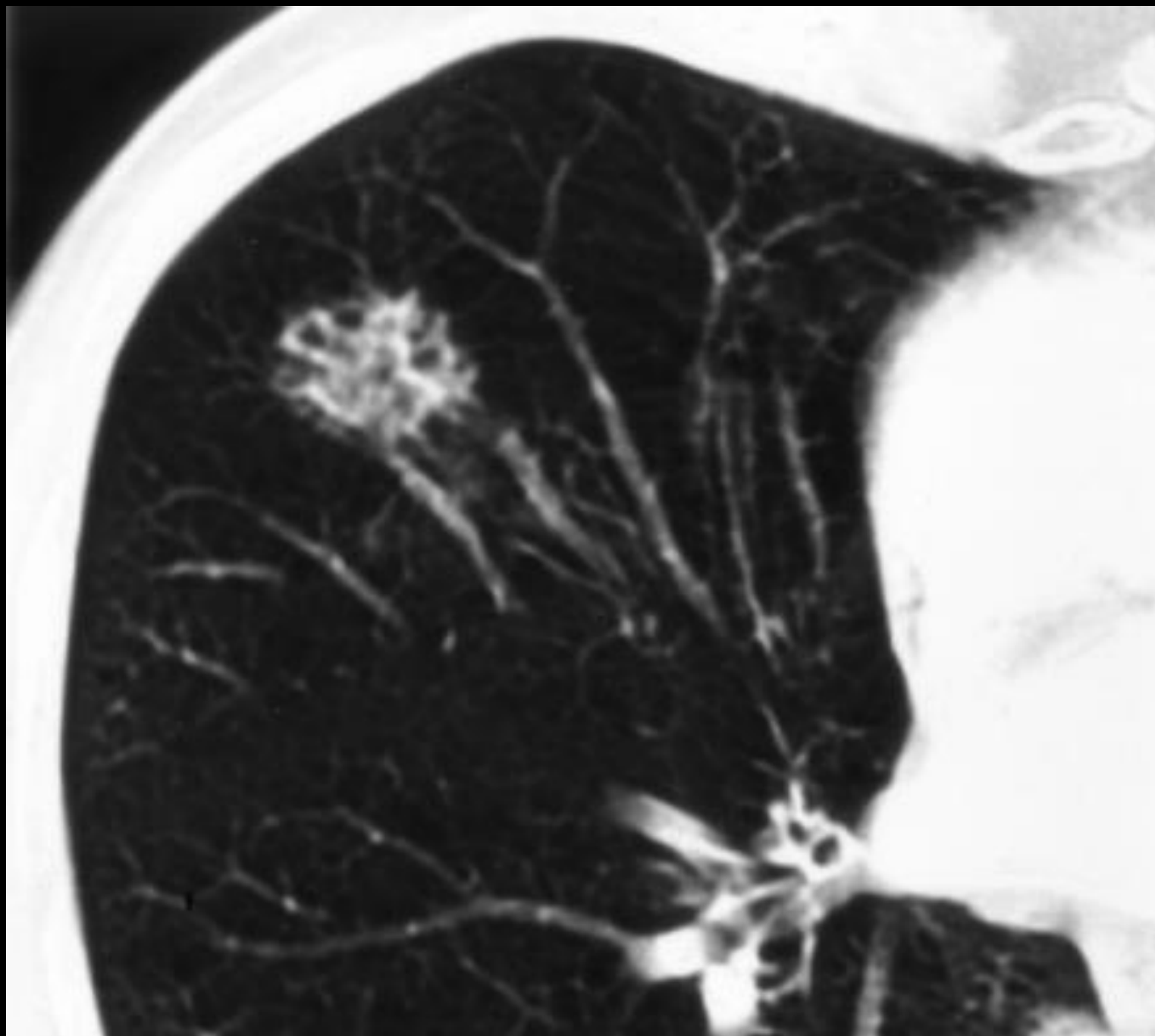
- Exception: metastases from liposarcoma or renal cell carcinoma



# Air bronchogram

- Air bronchogram (“bubble lucencies”, “pseudocavitation”) present in
  - 30% of malignant nodules (adenocarcinoma, lymphoma)
  - 6% of benign nodules

**Key point:** An air bronchogram within a nodule is an indicator for malignancy

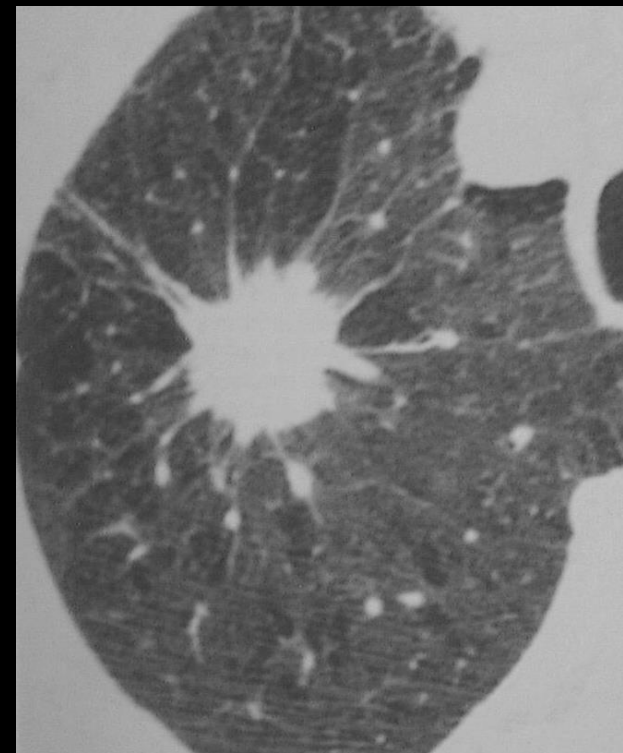
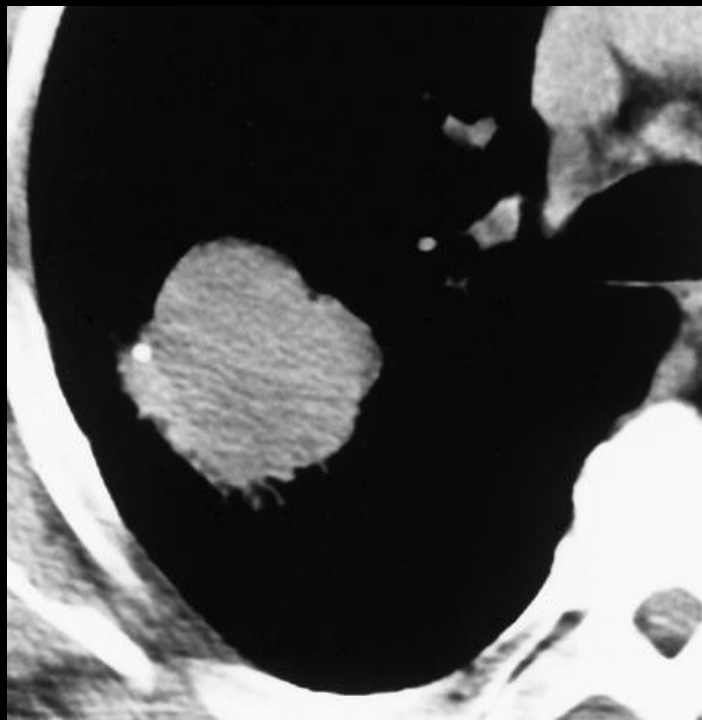
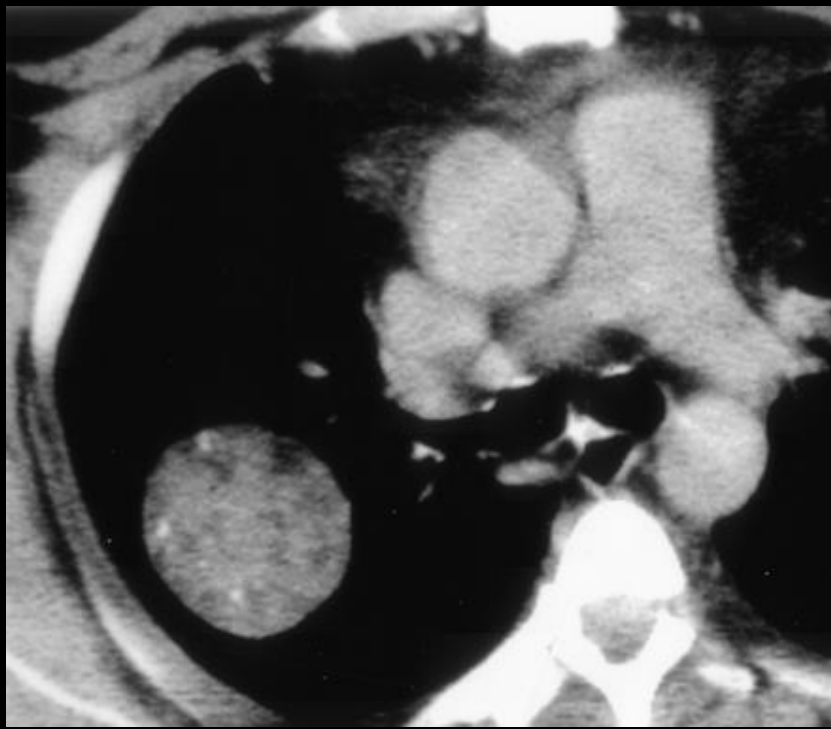


# Margin

- Benign
  - Smooth
  - But: 20-30% of malignant SPN are smoothly marginated (above all metastases)
- Malignant
  - Lobulated:
    - 82% malignant
  - Irregular:
    - 93% malignant
  - Spiculated:
    - 97% malignant

**Key point:** Assessment of margin characteristics is never a definitive discriminant criterion between benign and malignant nodules but may contribute in the probability of malignancy





# Location

- 70% of lung cancers are located in the upper lobes, most frequently in the right lung
- Benign nodules are equally distributed throughout the upper and lower lobes

**Key point:** Location alone cannot be used as a predictor of malignancy

- Exception: SPN oval or triangular,  $< 1$  cm, attached to fissure or pleura: most likely intrapulmonary LN

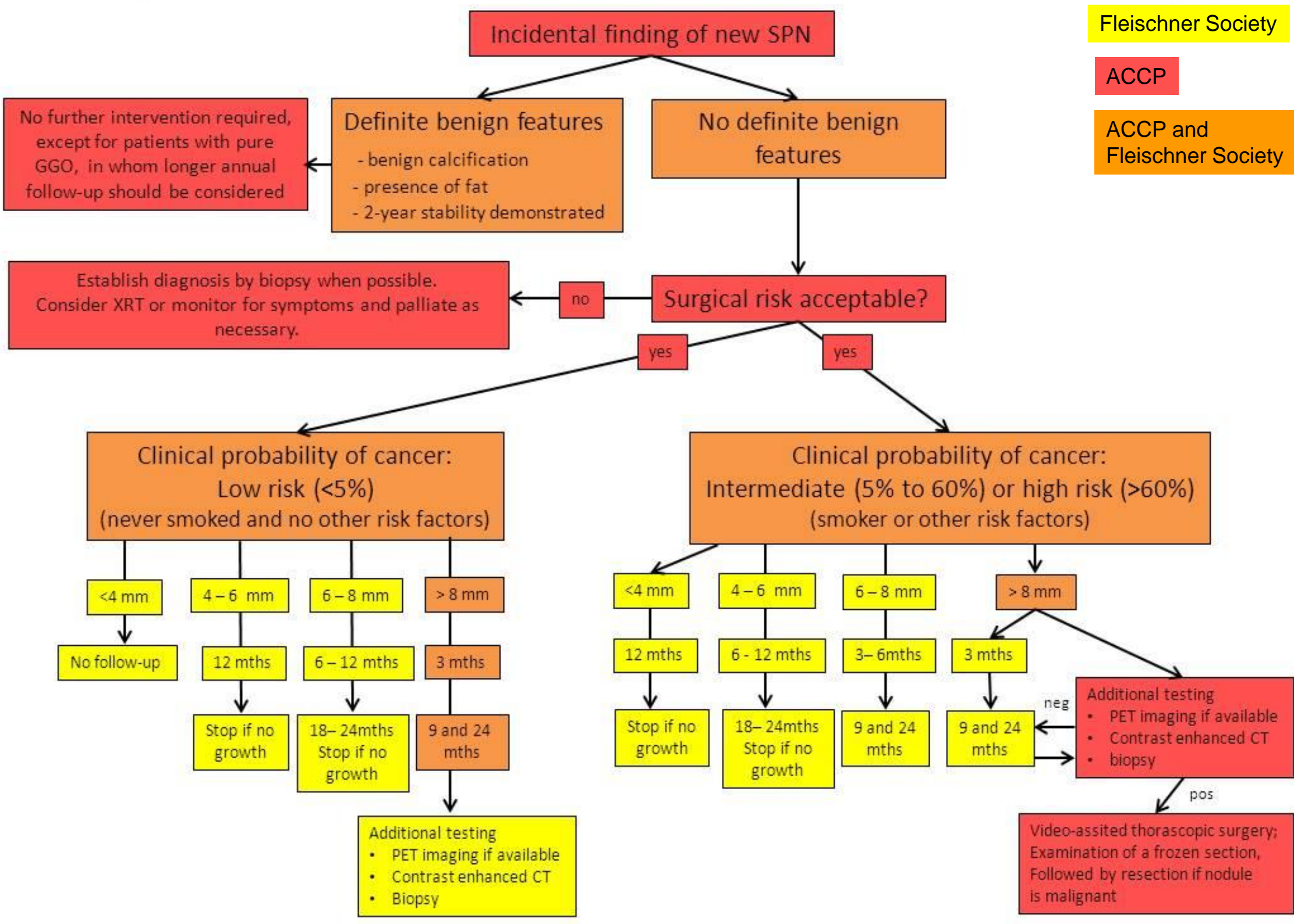
Table 6 Univariate analysis of predictive factors for IPLNs.

Variables	OR	95% CI	<i>p</i>
Age: <60 y	9.778	1.133–84.382	0.038
Sex: male	1.712	0.499–5.882	0.393
Number of nodules: single	2.893	0.432–19.385	0.274
Size: $\leq 5$ mm	3.947	0.749–20.811	0.106
Site: right	0.926	0.251–3.425	0.908
Location: lower	10.417	2.375–45.455	0.002
Border: clear	15.187	2.710–85.116	0.002
Distance from pleura: $\leq 10$ mm	2.667	0.518–13.699	0.241

CI = confidence interval; IPLN = intrapulmonary lymph node;  
OR = odds ratio.

Takenaka M, Asian Journal of Surgery 2013, 36:69-73





# Limitations of these guidelines

- Gender differences
  - a study cohort of 1520 patients showed that all bronchogenic tumour types (except a single case of large cell cancer) grew more slowly in women than in men with a mean difference in VDT of 454 days  
Lindell R M et al. Radiology 2007; 242;555-562
- 2-year stability is an accurate marker of benign disease
- The common situation of multiple incidental nodules

# Limitations of these guidelines

- 2-year stability as marker of benign disease
  - Determination of growth rate via assessment of volume doubling time
$$DT=(t \times \log 2) / \log (V_f / V_i)$$
  - Volume doubling time
    - Malignant: 30-400 days
    - Benign: < 30 or > 400 days
    - Stability for more than 2 years implies a volume doubling time of at least 730 days

**Key point:** stability over a 2 year period is considered to be a reliable indicator for a benign lesion



# Limitations of these guidelines

- 2-year stability as marker of benign disease

## Cave:

- Nodules < 3 cm diameter: volume vs diameter
  - A doubling in volume of a sphere corresponds to an increase of only 26% of its diameter (formula:  $V = \frac{4}{3}\pi r^3$ )
- some malignant nodules grow more slowly than others with some very long doubling times reported (over 3.5 years)

Takashima et al, 2004

- Ground-glass nodules and nodules with non-solid components tend to have longer doubling times than solid nodules

# Limitations of these guidelines

- Multiple incidental nodules

Relationship between nodule character and nodule size.

	Mean (mm)	Size of nodules (mm)			Total
		<5 (n = 57)	5–10 (n = 54)	>10 (n = 26)	
Benign (%)	6.4	53 (93%)	52 (96%)	4 (15%)	109 (80%)
Malignant (%)	17.0	4 (7%) <sup>a</sup>	2 (4%) <sup>b</sup>	22 (85%) <sup>a,b</sup>	28 (20%)
P-value	<0.0001	0.0001			

Note: This figure only includes nodules with definitive diagnosis.

<sup>a</sup>  $P < .0001$ .

<sup>b</sup>  $P < .0001$ .

Relationship between nodule character and distance from the nearest pleural surface.

	Mean (mm)	Distance (mm)			Total
		<5 (n = 59)	5–10 (n = 35)	>10 (n = 43)	
Benign (%)	8.3	54 (92%)	32 (91%)	23 (53%)	109 (80%)
Malignant (%)	18.4	5 (8%) <sup>a</sup>	3 (9%) <sup>b</sup>	20 (47%) <sup>a,b</sup>	28 (20%)
P-value	<0.0001	<0.0001			

Note: This figure only includes nodules with definitive diagnosis.

<sup>a</sup>  $P = .0003$ .

<sup>b</sup>  $P = .0008$ .

# Limitations of these guidelines

- Multiple incidental nodules

Frequency of malignant nodule based on size and distance from the nearest pleural surface.

		size (mm)		
		<10	10 $\geq$	Total
Distance (mm)	<10	3/86 <sup>a,b,d</sup> (3%)	5/8 <sup>a,e</sup> (63%)	8/94 (9%)
	10 $\geq$	3/25 <sup>c,d</sup> (12%)	17/18 <sup>b,c,e</sup> (94%)	20/43 (47%)
	Total	6/111 (5%)	22/26 (85%)	28/137 (20%)

<sup>a</sup>  $P < .0001$ .

<sup>b</sup>  $P < .0001$ .

<sup>c</sup>  $P < .0001$ .

<sup>d</sup>  $P = .126$ .

<sup>e</sup>  $P = .072$ .

# Limitations of these guidelines

Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society.

Naidich DP, Bankier AA, MacMahon H, Schaefer-Prokop CM, Pistoletti M, Goo JM, Macchiarini P, Crapo JD, Herold CJ, Austin JH, Travis WD.

Radiology. 2013 Jan;266(1):304-17. doi: 10.1148/radiol.12120628. Epub 2012 Oct 15.

PMID: 23070270 [PubMed - indexed for MEDLINE]

## Recommendations for the Management of Subsolid Pulmonary Nodules Detected at CT: A Statement from the Fleischner Society

Nodule Type	Management Recommendations	Additional Remarks
<b>Solitary pure GGNs</b>		
≤5 mm	No CT follow-up required	Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN
>5 mm	Initial follow-up CT at 3 months to confirm persistence then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Solitary part-solid nodules	Initial follow-up CT at 3 months to confirm persistence. If persistent and solid component <5 mm, then yearly surveillance CT for a minimum of 3 years. If persistent and solid component ≥5 mm, then biopsy or surgical resection	Consider PET/CT for part-solid nodules >10 mm
<b>Multiple subsolid nodules</b>		
Pure GGNs ≤5 mm	Obtain follow-up CT at 2 and 4 years	Consider alternate causes for multiple GGNs ≤5 mm
Pure GGNs >5 mm without a dominant lesion(s)	Initial follow-up CT at 3 months to confirm persistence and then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Dominant nodule(s) with part-solid or solid component	Initial follow-up CT at 3 months to confirm persistence. If persistent, biopsy or surgical resection is recommended, especially for lesions with >5 mm solid component	Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for lung cancer

**Note.**—These guidelines assume meticulous evaluation, optimally with contiguous thin sections (1 mm) reconstructed with narrow and/or mediastinal windows to evaluate the solid component and wide and/or lung windows to evaluate the nonsolid component of nodules, if indicated. When electronic calipers are used, bidimensional measurements of both the solid and ground-glass components of lesions should be obtained as necessary. The use of a consistent low-dose technique is recommended, especially in cases for which prolonged follow-up is recommended, particularly in younger patients. With serial scans, always compare with the original baseline study to detect subtle indolent growth.

# Conclusion

- **Pulmonary nodules are**
  - a common finding on CT in smokers and non-smokers
  - are frequently multiple
  - are usually smaller than 1 cm in diameter
- **Guidelines to manage these nodules**
  - The Fleischner Society's recommendations:
    - MacMahon H et al. Radiology 2005; 237:395-400*
    - Naidich DP et al. Radiology 2013; 266(1):304-317*
  - ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition): 2007
    - Gould M K et al. Chest 2007;132:108S-130S*
  - Features of benign nodules and pretest probability
  - Used for incidental / indeterminate nodules



**Thank you for your attention**

**W De Wever**

**University Hospitals - Dept of Radiology  
Leuven, Belgium**

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