The Evaluation and Management of the Solitary Pulmonary Nodule

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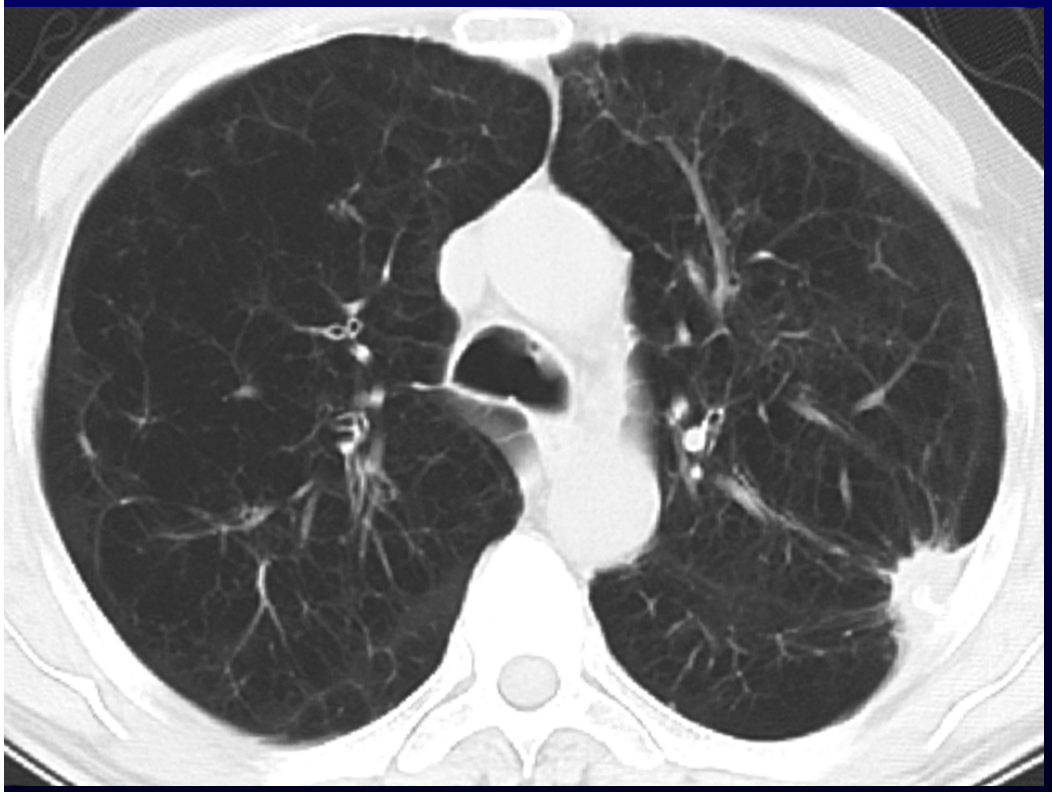
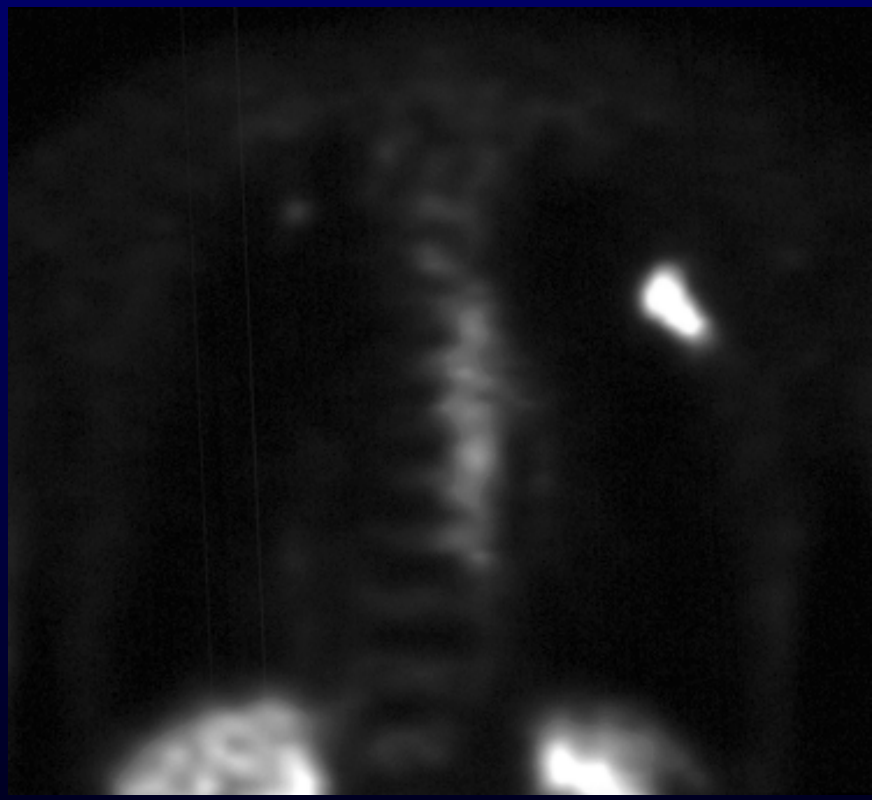
Case Presentation

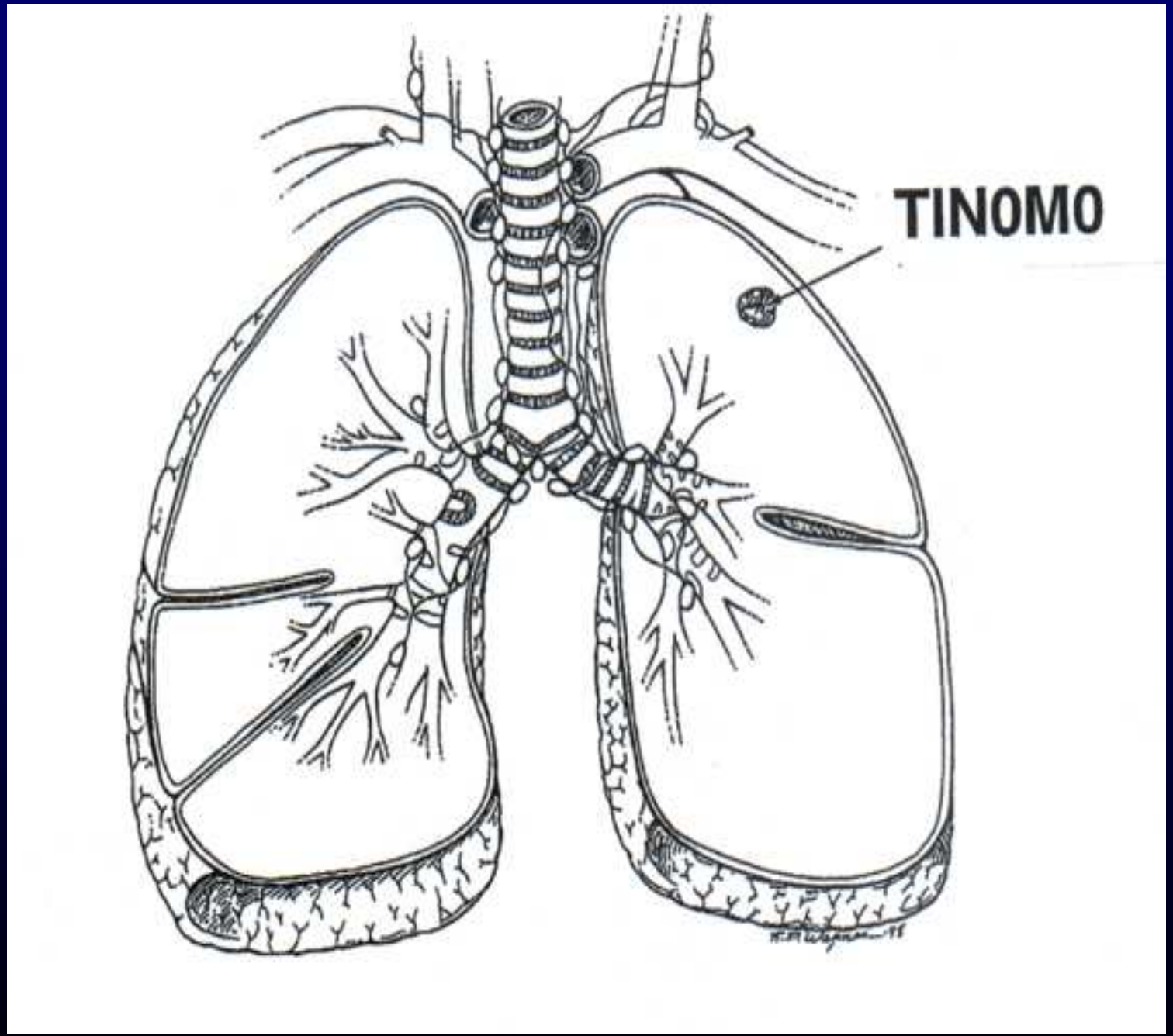
- 56 year old female has preoperative CXR for elective surgery
- 60 pack year history of smoking
- Asymptomatic
- Family history positive for lung cancer
- Referred for abnormal CXR





Management Alternatives

- Surgery
  - "When in doubt, cut it out"
- Biopsy
  - "When cancer is the answer, tissue is the issue"
- Wait and watch
  - "Don't just do something…stand there!"


TINOMO

SPN Defined

- Single, spherical, well circumscribed radiographic opacity
- Measures up to 3 cm in diameter
- Completely surrounded by aerated lung
- No atelectasis, pneumonia, hilar enlargement or pleural effusion
- Usually asymptomatic

Ost et al. N Engl J Med 2003;348:2535-42.

More Definitions

- Sub-centimeter nodule (<8-10 mm)
- Nodule (8-30 mm)
- Indeterminate nodule: not calcified in a benign pattern or proved stable over 2 years of follow-up
- Mass (>30 mm)
  - 80-90% are malignant
- Old estimates put the number at about 150,000 annually

What about CT?

- Approximately 60 million CT exams in US annually
- ~ 15% include the chest
- 20-50% screening studies at least 1 nodule
- 1-2 million new nodules per year!

What if we screened?

- 9 million people fit criteria for NLST
- First year 2.25 million nodules (>4mm)

Why is the SPN Important?

- Some nodules are cancer, some are not …
- Prevalence of lung cancer:
  - 46% to 82% in recent studies of PET imaging
  - 2% to 13% in recent studies of CT screening
- Lower in areas where endemic mycoses and TB are highly prevalent
- Under 35; ~ 1 % malignant
- CT surgical series ~ 80% malignant
- In known extra-thoracic malignancy, a *solitary* nodule is more likely to represent a second primary lesion than metastasis

Why is the SPN Important?

- Malignant nodules represent a potentially curable form of lung cancer:
  - 5-year survival for patients with malignant SPN 65% to 80%
  - 5-year survival for unselected patients with lung cancer 12% to 15%

Mountain CF. Chest 1997;111:1710
Ginsberg et al. J Thorac Cardiovasc Surg 1983;86:654
Inoue et al. J Thorac Cardiovasc Surg 1998;116:407

Differential Diagnosis: Benign SPN

- Non-specific or healed granulomas (25%)
- Infectious granulomas (15%)
- Benign neoplasms (15%)
  - Hamartoma
  - Lipoma, fibroma, countless others (rare)
- Others: lung abscess, pseudotumor, round atelectasis, AVM, infarct, mucoid impaction, hematoma, rheumatoid nodule, Wegener's

Differential Diagnosis: Malignancy

- Adenocarcinoma (~50%)
  - Bronchoalveolar cell carcinoma (~5%)
- Squamous cell carcinoma (~20%)
- Solitary metastasis (~10%)
- Undifferentiated NSCLC (~10%)
- Small cell carcinoma (<2%)

SPN Management Goals

- To diagnose malignant nodules promptly, in order to permit timely surgical resection
- To correctly identify active inflammatory or infectious processes
- To avoid surgery (when possible) in patients with benign nodules

Management

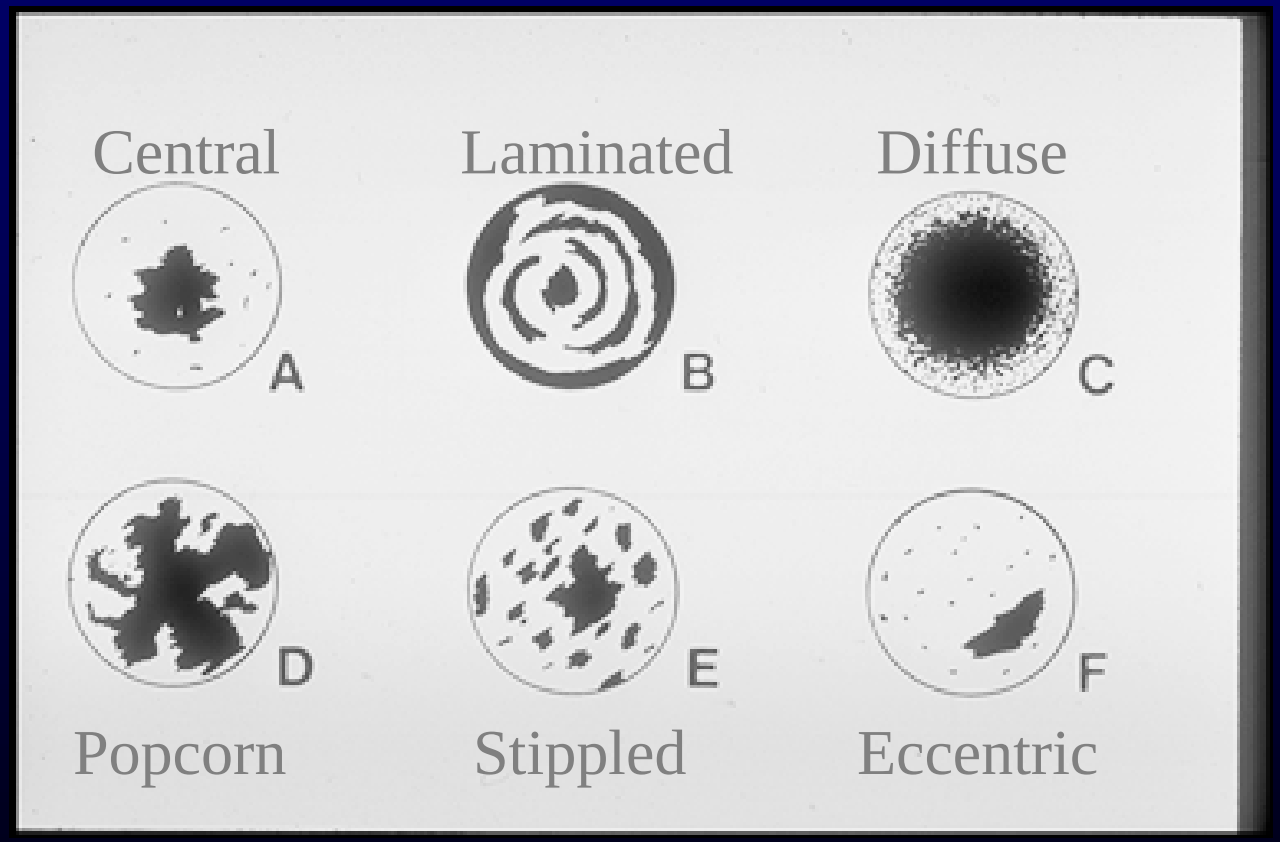
- Estimate clinical “pre-test” probability
- Obtain/review imaging tests
  - CXR
  - CT
  - FDG-PET
- Consider surgical risk
- Elicit patient preferences
- Select surgery, biopsy or “watchful waiting”

Pre-test Probability

- Facilitates selection and interpretation of subsequent tests
- Validated model from Mayo Clinic
  - Six independent predictors of malignant SPN
  - Patient characteristics: Age, smoking status, history of extrathoracic malignancy
  - Nodule characteristics: diameter, spiculation, upper lobe location

Swensen et al. Arch Intern Med 1997;157:849

CXR: Patterns of Calcification



Patterns A-D are benign; patterns E and F are non-specific

Computed Tomography

- Confirms intraparenchymal location
- Identifies other nodules
- Provides “road map” for subsequent tests
- Gives more accurate information about size and edge characteristics
- May reveal occult calcification

CT: Size Matters

Size	% malignant
<4 mm	0%
4-7 mm	0.8%
8-20 mm	22%
>20 mm	63%

Swensen et al. AJRCCM 2002;165:508-13.

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MEDICAL UNIVERSITY OF SOUTH CAROLINA

Size

- Screening
- < 3 mm malignancy risk of 0.2%
- 4-7 mm malignancy risk of 0.9%
- Mayo CT Screening Trial

- 2408 Nodules
- ≤ 4 mm malignancy risk of 0.2%
- 4-10 mm malignancy risk 1%
- McWilliams J Thorac Oncol 2006;1:61-68

CT: Edge Characteristics

Border type	LR
1. Smooth	0.2
2. Lobulated	0.5
3. Spiculated	5.0
4. Corona radiata	14

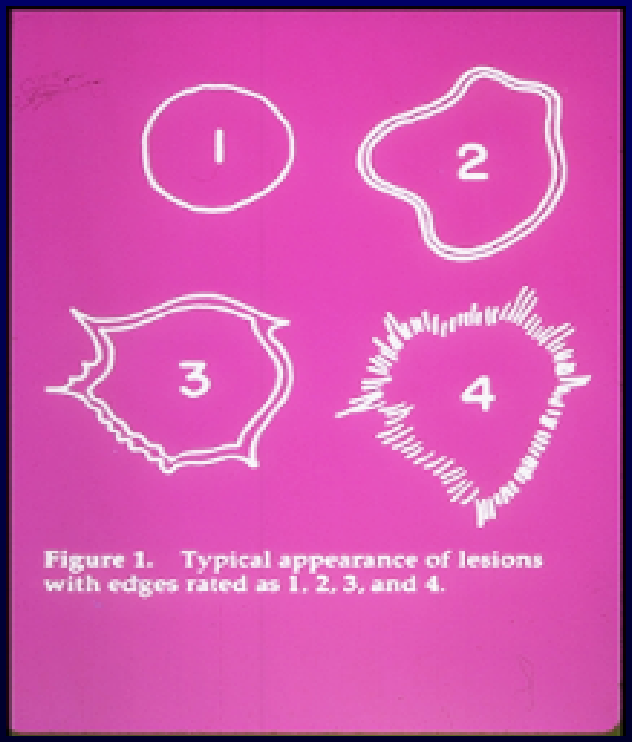


Figure 1. Typical appearance of lesions with edges rated as 1, 2, 3, and 4.

Siegelman et al. Radiology 1986;160:307

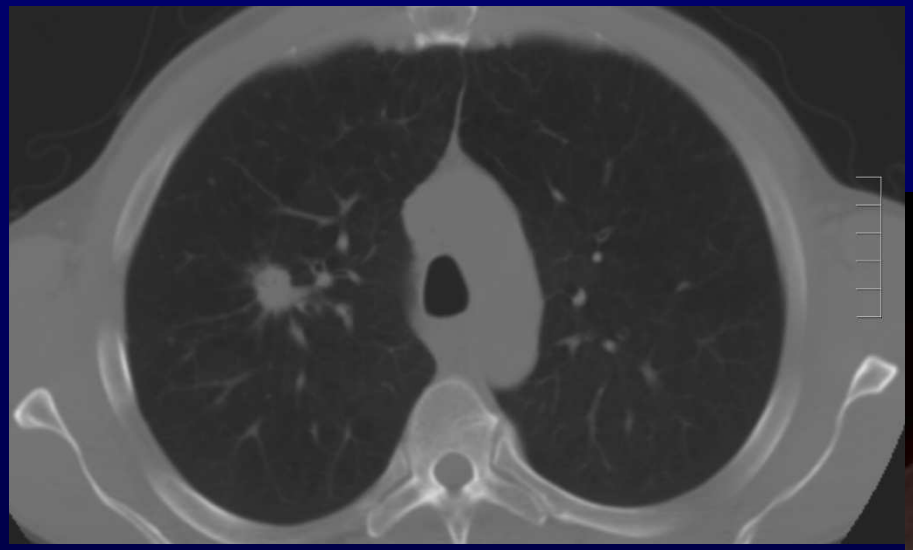
FDG-PET Imaging

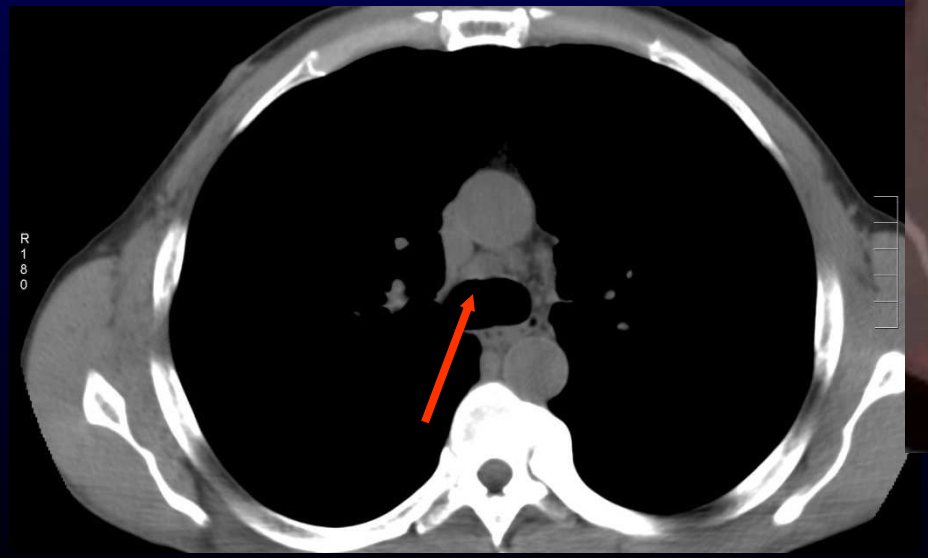
- Non-invasive, functional imaging test
- FDG accumulates in metabolically active tumor cells
- Sensitivity ~87%, specificity ~83%
- False negative results:
  - Small nodules <8 mm to 10 mm
  - Well-differentiated adenocarcinoma, BAC, carcinoid
- False positive results:
  - Granulomatous infection/inflammation

Lowe and Naunheim. Thorax 1998;53:703-12.
Wahidi et al. Chest 2007.

FDG-PET Imaging

- In patients with low to moderate pre-test probability of malignancy (5% to 60%) and an indeterminate SPN > 8 mm to 10 mm in diameter, we recommend that FDG-PET imaging should be performed to characterize the nodule. Grade 1B.
- **Recommendation 10**: In patients with a SPN that has a high pre-test probability of malignancy (>60%), or patients with a sub-centimeter nodule that < 8 mm to 10 mm in diameter, we suggest that FDG-PET should not be performed to characterize the nodule. Grade 2C.

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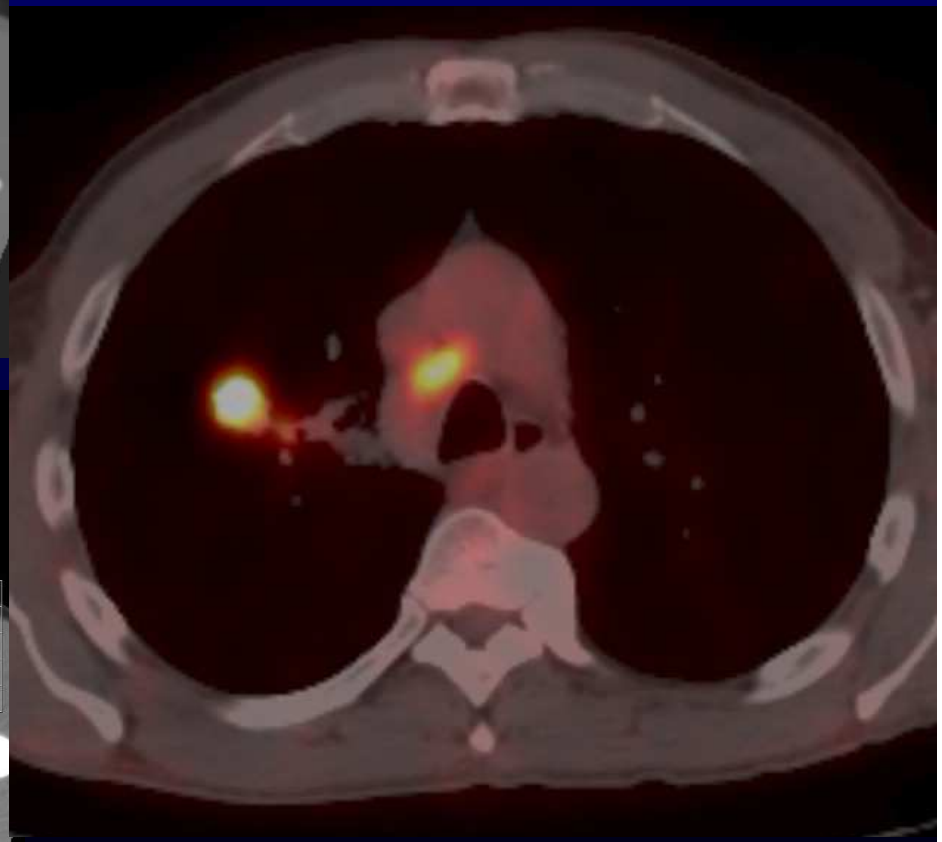


SPN Management

Recommendation 11: In every patient with a SPN, we recommend that clinicians discuss the risks and benefits of alternative management strategies and elicit patient preferences. Grade of recommendation: 1C

Observation (“Wait and Watch”)

- Optimal time interval between repeat imaging studies not known
- Growth at any time is presumptive evidence of malignant SPN and should prompt surgical referral
- Delay in diagnosis of malignant SPN may lead to disease progression and missed opportunity for cure
- Magnitude of risk not known

Observation

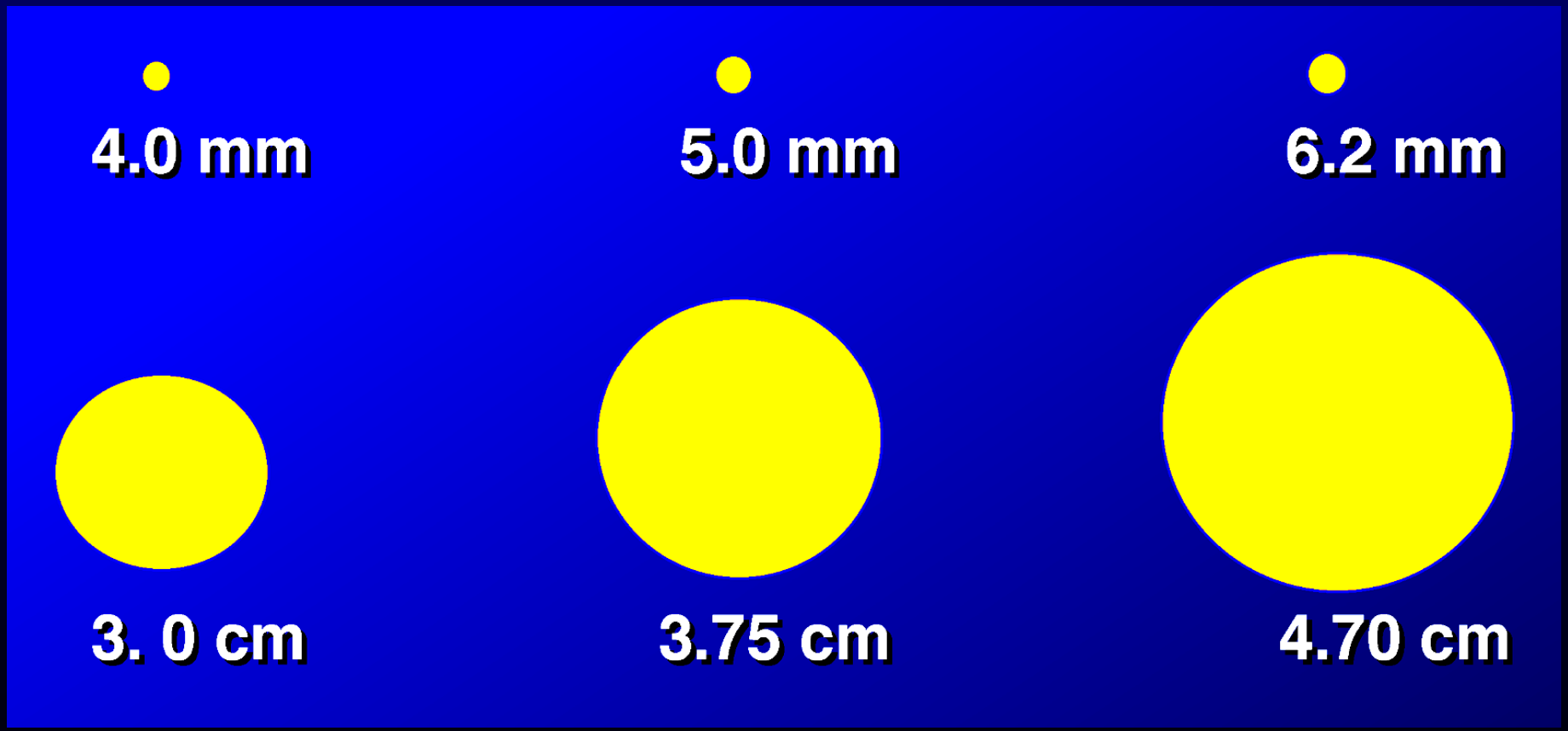
ACCP Rec: In patients with an indeterminate SPN at least 8 mm to 10 mm, observation with serial CT scans is an acceptable:

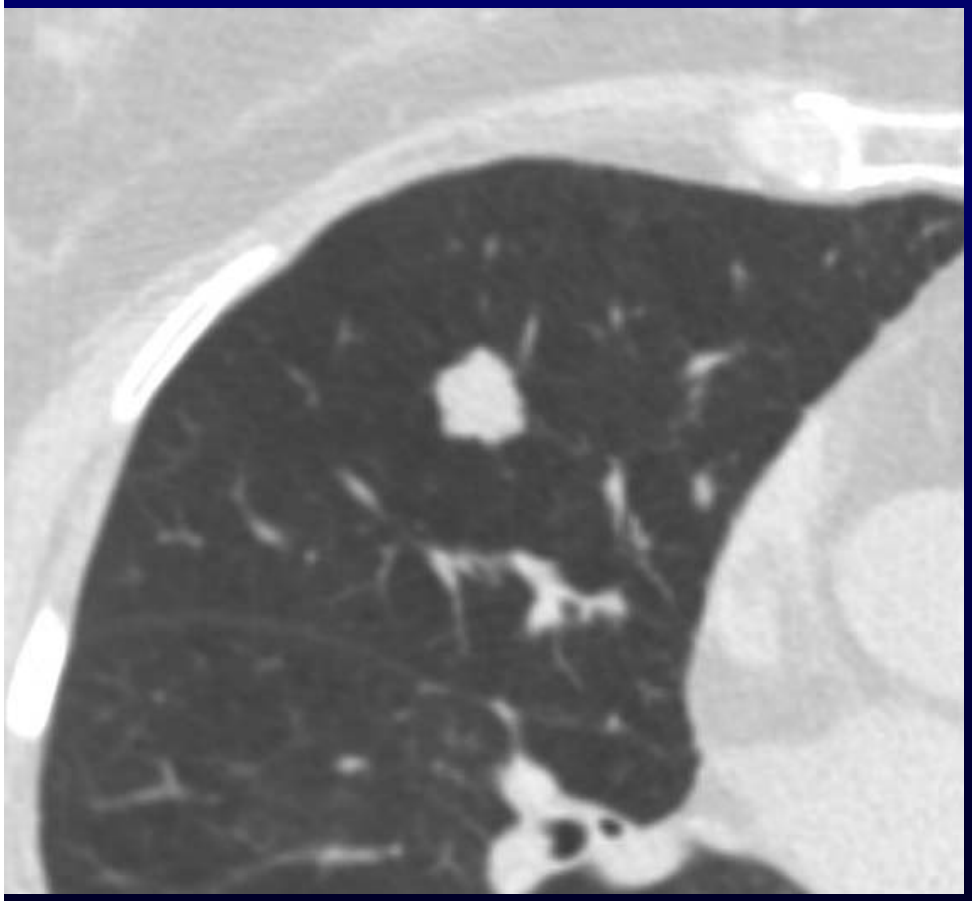
- when the probability of malignancy is very low (<5%)
- when clinical probability is low (<30% to 40%), and the lesion is not hypermetabolic by FDG-PET
- when needle biopsy is non-diagnostic and the lesion is not hypermetabolic by FDG-PET
- when a fully informed patient prefers this non-aggressive management approach. (Grade 2C)

Doubling Time

- Specifically refers to ***VOLUME***
- $4/3\pi r^3$
- 26% diameter change equals 1 doubling
- Lung Cancer 30-1200 days (median 120)
- Range of 2.5-40 years for tumor to reach 1 cm
- Benign lesions < 30 days or > 465 days

DOUBLING TIME





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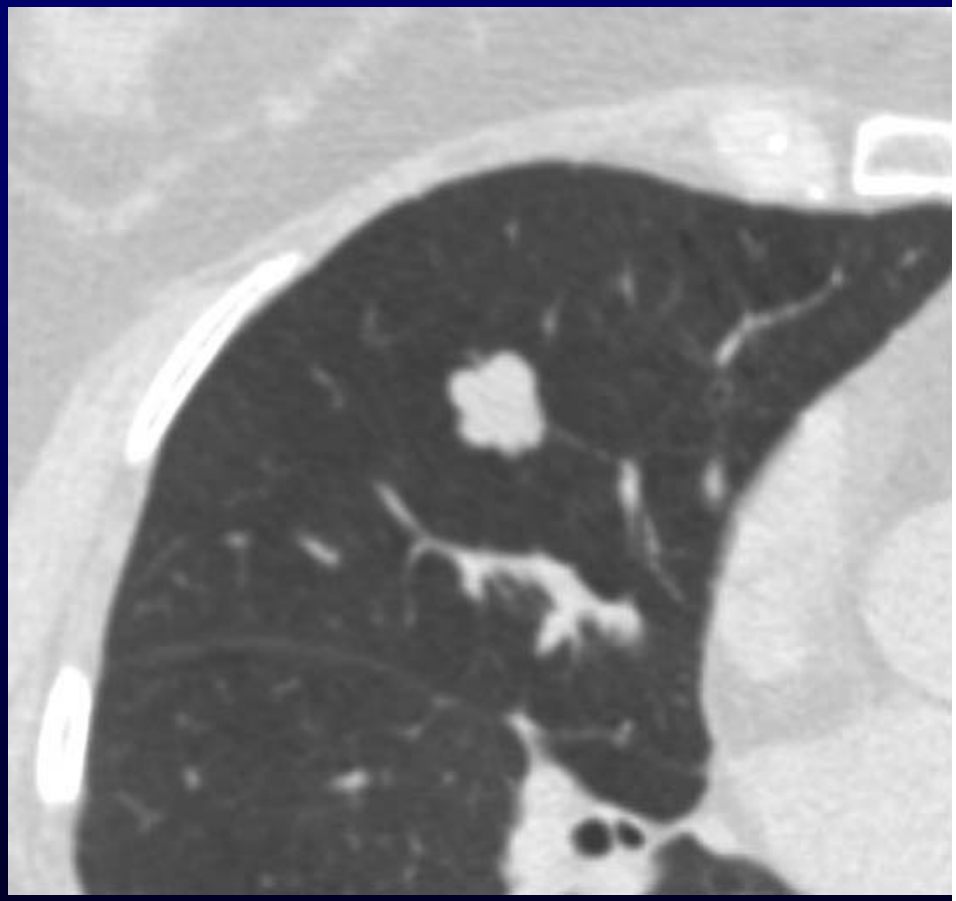

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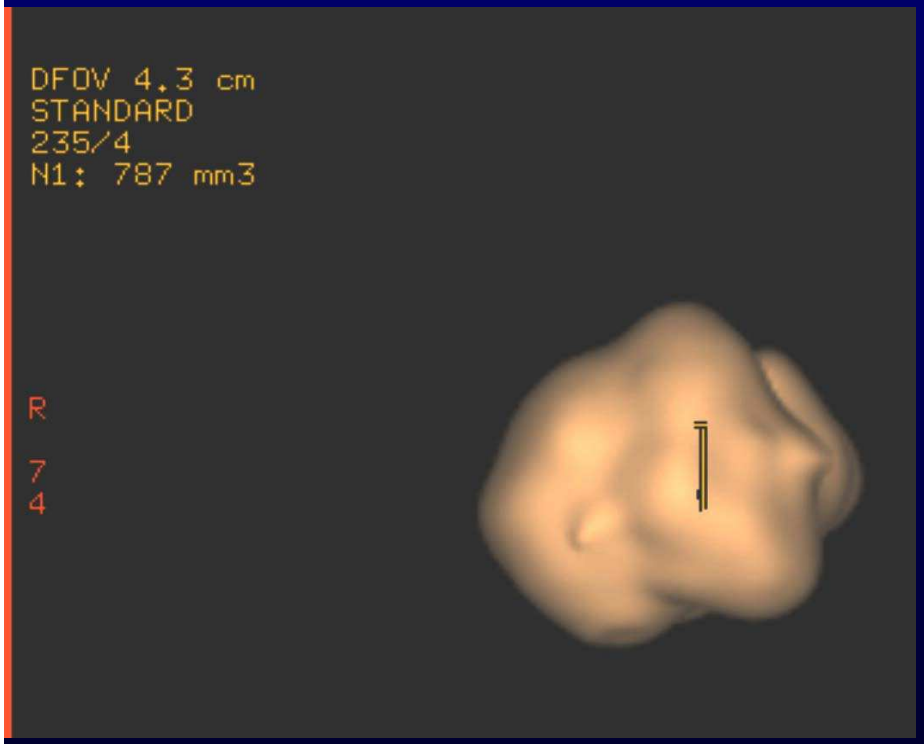
DFOV 4.3 cm
STANDARD
235/4
N1: 787 mm3
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7
4

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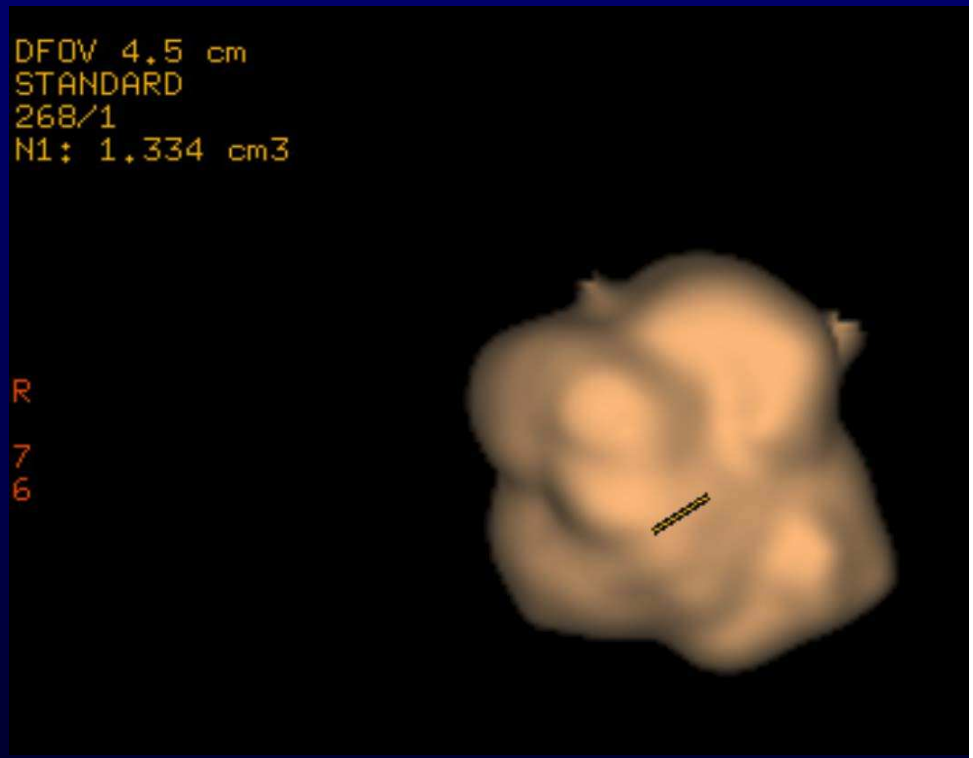

DFOV 4.5 cm
STANDARD
268/1
N1: 1.334 cm3
R
7
6

9/05

Doubling Time

- 20 doublings = 1mm
- 30 doublings = 1 cm
- 40 doublings =10 cm

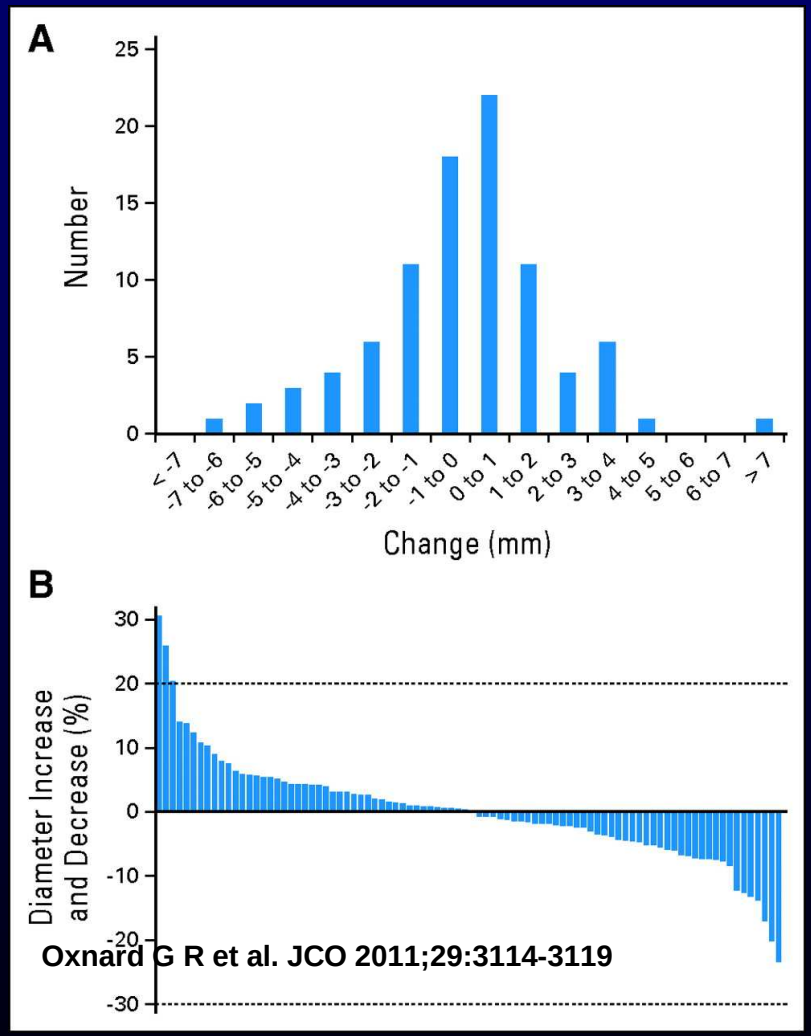
- Over 50% of the life of a malignancy is spent at an undetectable size
- For ground glass and part-solid nodules density change may be more important

Variablility of Tumor Measurement on Repeat CT within 15 minutes

- 33 patients with NSCLC
- Repeat CT within 15 min.
- 57% 1mm difference
- 33% 2mm difference
- 23% shrinkage to 33% growth.

- JCO 2011, 29:311

Distribution of measurement changes found on repeat computed tomography scans performed within 15 minutes of each other, in millimeters; there was a greater than 1-mm magnitude of change in the majority of lesions (57%).



Oxnard G R et al. JCO 2011;29:3114-3119

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Subcentimeter Nodules

- Measure <8 to 10 mm in diameter
- Poorly characterized by CT and PET
- Difficult to biopsy
- Low prevalence of malignancy
  - <1% when diameter <5 mm
  - 2.3% to 6% when diameter 5 to 9 mm
- Serial CT typically used to identify growth

Subcentimeter Nodules

ELCAP: 233 nodules on baseline CT scan

- 189 solid nodules (7% malignant)
- 16 semisolid nodules (63% malignant)
- 28 pure ground-glass opacity (18% malignant)

Henschke et al. AJR 2002; 178:1053-1057.

60% of GGO malignant in other studies

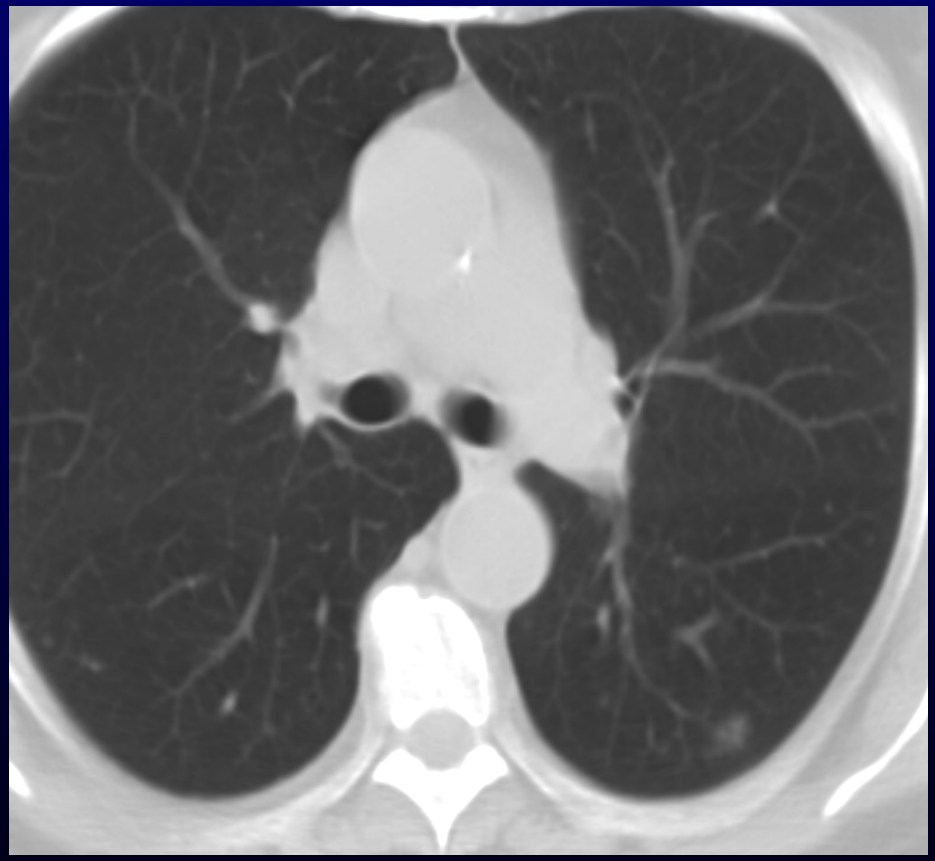
Takashima et al. AJR 2003;180:1255.

Li et al. Radiology 2004;233:793.

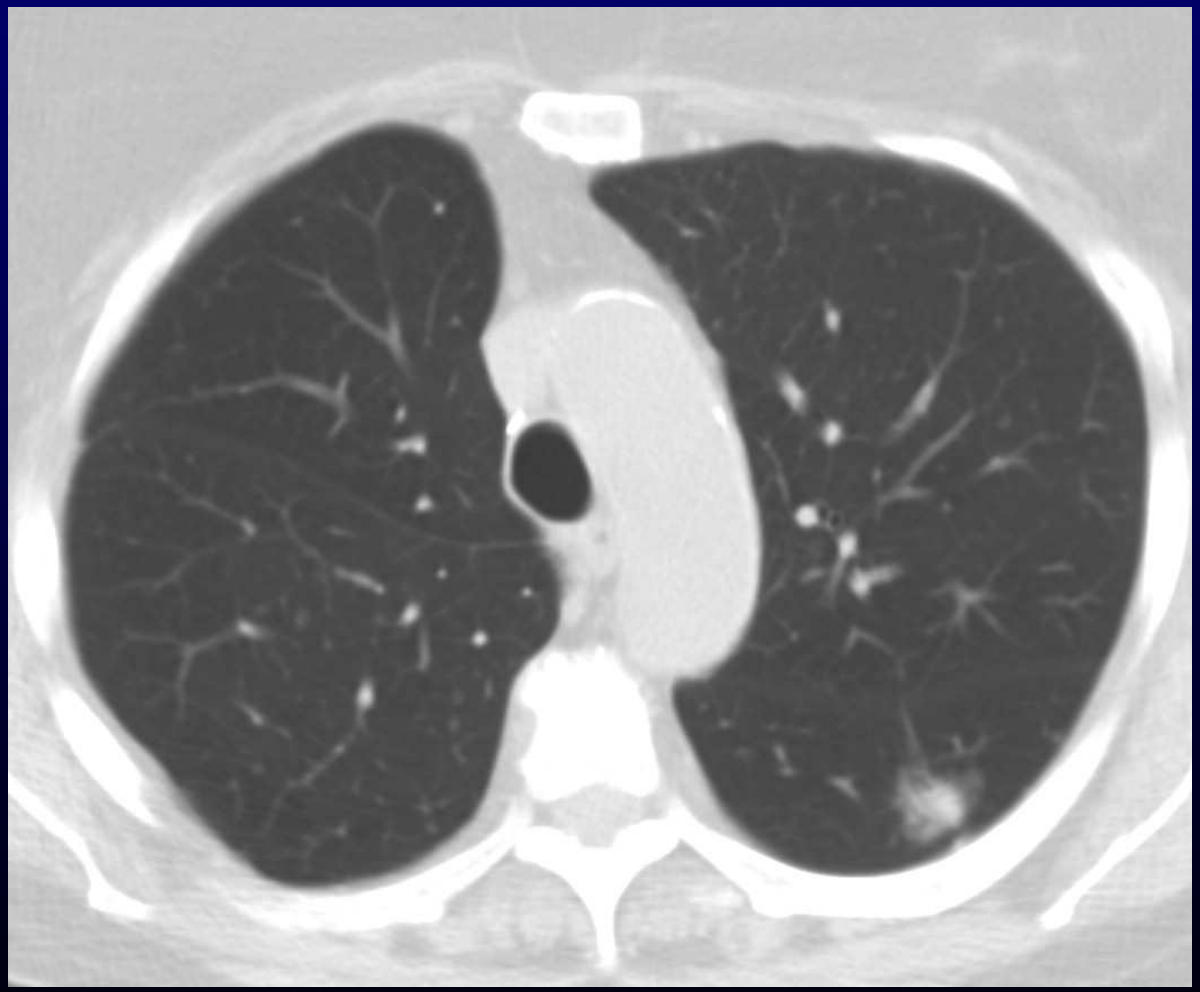
Sub-Types of Nodules

- Solid
- Part-solid
- Ground glass

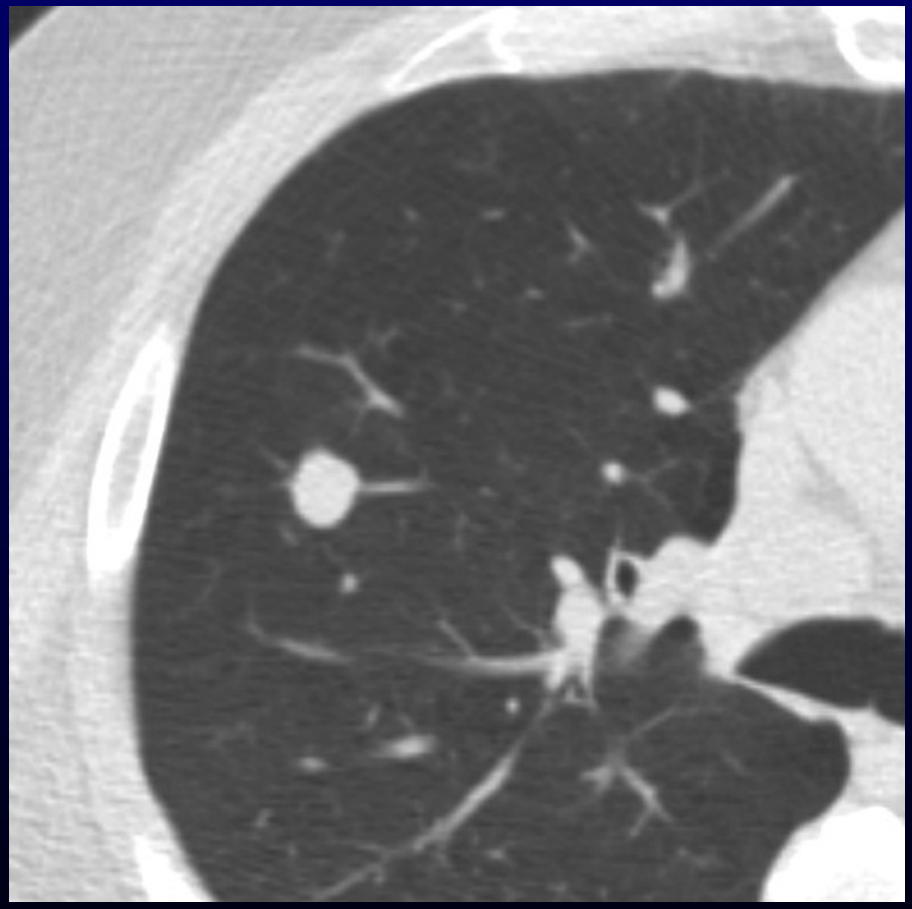
Ground Glass Nodule



Part-Solid Nodules



Solid Nodules



Morphology, Pathology and Growth

	Pathology	TVDT (days)
Pure GGO	AAH→BAC	~800
Semi-solid	BAC→Adenocarcinoma; Squamous; Small cell	~450
Solid	Adenocarcinoma; Squamous, Small cell	~150

Favorable Prognosis in GGOs

- 69 cancers with large GGO component (47 BAC)
- All stage I, no evidence of recurrence at 35 months of follow-up

  Suzuki et al. Ann Thorac Surg 2002; 74:1635-1639.

- 17 GGO with wedge or segmentectomy
- No recurrence at 32 months of follow-up

  Watanabe S et al. Ann Thorac Surg 2002; 73:1071.

Subcentimeter Nodules: Management Considerations

- Minimize radiation exposure by limiting dose and frequency of exams, while identifying growth as early as possible
- Frequency of recommended follow-up depends on:
  - Risk factors for cancer
  - Size of nodule
  - Nodule morphology
  - Technical limitations in identification of growth
  - Comorbidities and surgical risk

Size	Low Risk	High Risk
≤4mm	No f/u	f/u 12 months
4-6 mm	f/u 12 months	f/u 6-12 months up to 2 years
6-8 mm	f/u 6-12 months up to 2 years	f/u 3-6 months
>8 mm	f/u 3, 9, 24 mos./consider PET or biopsy	

Ground glass and part-solid nodules may require follow-up greater than 2 years to exclude indolent adenocarcinomas

CT-Guided FNA

11 studies with data about accuracy in SPN:

- Median sensitivity 90% (range 65% to 94%)
- Median specificity 100% (range 96% to 100%)
- Specificity assumed to be 100% in some studies
- Non-diagnostic results 5x more common in benign than malignant nodules, but non-diagnostic biopsy does not rule out malignancy
- Median probability of PTX 26.5% (range 15% to 43%)
- ~5% required chest tube (range 4% to 18%)

Wahidi et al. Chest 2007.

Biopsy: TTNA

ACCP recs: In patients with an indeterminate SPN > 8 - 10 mm it is appropriate to perform a TTNA or bronchoscopy in the following circumstances:

- when clinical pre-test probability and findings on imaging tests are discordant, for example, when the pre-test probability of cancer is high and the lesion is not hypermetabolic by PET
- when a benign diagnosis requiring specific medical treatment is suspected
- when a fully informed patient desires proof of a malignant diagnosis prior to surgery, especially when the risk of surgical complications is high.
- Patient non operative and need tissue to rx

Surgery

- Gold standard for diagnosis and treatment
- VATS biopsy for peripheral lesions
  - Convert to thoracotomy with lobectomy and mediastinal lymph node dissection if frozen section reveals cancer
  - Mortality ~1%
  - VATS lobectomy (with LN dissection) requires special expertise
- Limited resection for marginal surgical candidates
- Thoracotomy may be required for deeper lesions
  - Morbidity 30%
  - Mortality 2% to 4%

Surgery

ACCP REC: In surgical candidates with indeterminate SPN 8 mm to 10 mm, surgical diagnosis is preferred in most circumstances, including:

- when the clinical probability of malignancy is moderate to high (>60%)
- when the nodule is hypermetabolic by FDG-PET imaging
- when a fully informed patient prefers undergoing a definitive diagnostic procedure

Grade of recommendation: 1C

Back to our patient…

- Patient was discussed at combined thoracic oncology tumor board
- Pre test probability for cancer felt to be very high
- Patient offered and agreed to surgery
- Underwent an uncomplicated wedge resection
- Dx -- Sarcoidosis

Conclusion

- Common Radiologic Problem with an Increasing incidence
- Multiple Imaging Strategies
- Multiple minimally invasive and surgical approaches
- Management Decisions Often Based on Pre-test Probability of Malignancy


Charleston