

## The Newly Discovered Pulmonary Nodule What to do?

**Steven M. Keller, M.D.**

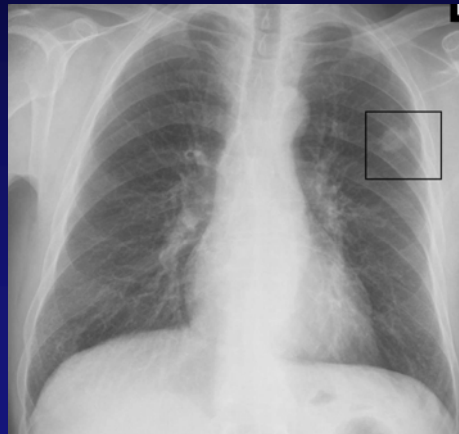
Director Thoracic Surgery, Weiler Hospital  
Professor of Cardiothoracic Surgery  
Albert Einstein College of Medicine  
Montefiore Medical Center, New York

## Solitary Pulmonary Nodule Definition Nomenclature Committee of the Fleischner Society

- Round opacity, at least moderately well marginated and no greater than 3 cm in maximum diameter
- Some authors use the modifier “small” if the maximum diameter of the opacity is less than 1 cm
- A micronodule is less than 3 mm in diameter

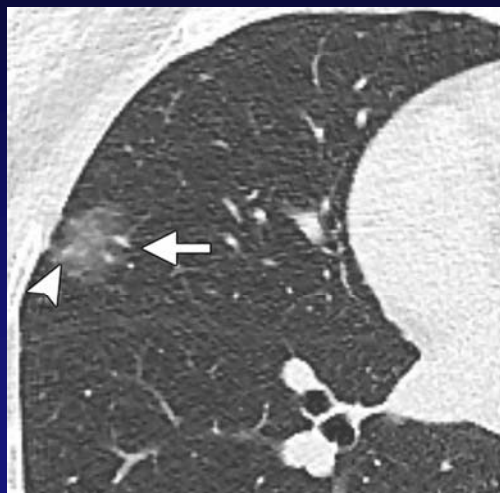
Radiology 1996; 200(2):327-31

## Your Father's (Grandfather's) Solitary Pulmonary Nodule



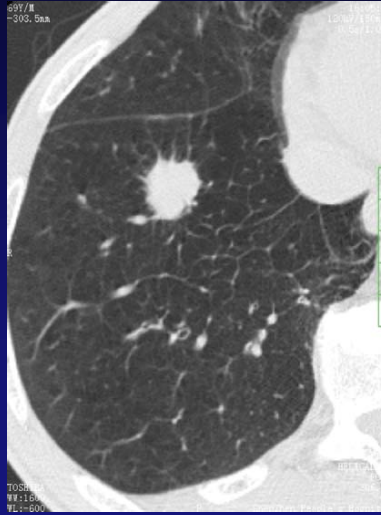
## The Millennial's Solitary Pulmonary Nodule

- **SubSolid**
  - *Ground-glass nodule (synonym, nonsolid nodule)* manifests as hazy increased attenuation in the lung that does not obliterate the bronchial and vascular margins
  - *Partially solid nodule (synonym, semisolid nodule)* consists of both ground-glass and solid soft-tissue attenuation components



## The Millennial's Solitary Pulmonary Nodule

- **Solid nodule**
  - Spiculated homogenous soft-tissue attenuation



Wang. J Thorac Dis 2014;6;872-7

## Differential Diagnosis of Solid Pulmonary Nodules

- Neoplastic
  - Primary lung – non small cell, small cell, carcinoid, lymphoma
  - Solitary metastases
- Benign – hamartoma, AV malformations
- Infectious – granuloma, round pneumonia, abscess, septic emboli
- Non-infectious – subpleural lymph node, rheumatoid nodule, Wegener, focal scarring
- Congenital – sequestration, bronchogenic cyst

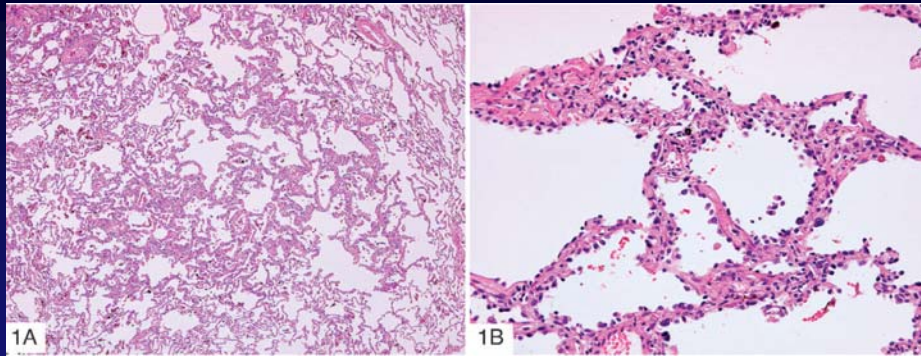
## Differential Diagnosis of Subsolid Pulmonary Nodules

- Neoplastic
  - Primary lung – adenocarcinoma,
  - Solitary metastases – melanoma, RCC, pancreas, breast, GI, lymphoproliferative
- Benign – organizing pneumonia, focal interstitial fibrosis, endometriosis

## Bronchoalveolar Carcinoma R.I.P.

- Atypical Adenomatous Hyperplasia (AAH) - localized, small (usually 0.5 cm or less) proliferation of mildly to moderately atypical type II pneumocytes and/or Clara cells lining alveolar walls and sometimes, respiratory bronchioles

## Atypical Adenomatous Hyperplasia (AAH)

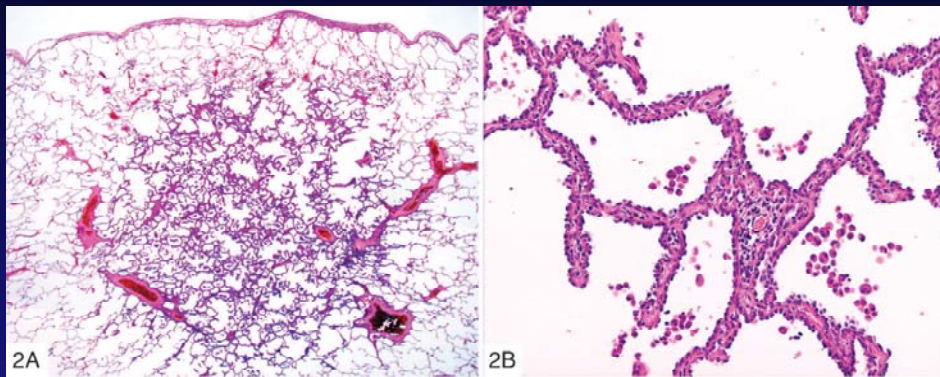


Travis. Arch Pathol Lab Med 2013;137:685-705

## Bronchoalveolar Carcinoma R.I.P.

- Adenocarcinoma in situ - localized small (3 cm) adenocarcinoma with growth restricted to neoplastic cells along preexisting alveolar structures (lepidic growth), lacking stromal, vascular, or pleural invasion. Papillary or micropapillary patterns and intra-alveolar tumor cells are absent

## Adenocarcinoma *in situ*

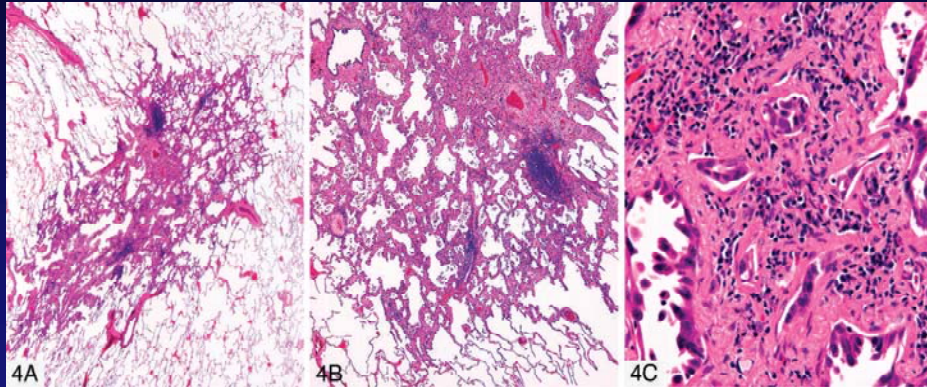


Trevis. Arch Pathol Lab Med 2013;137:685-705

## Bronchoalveolar Carcinoma R.I.P.

- Minimally invasive adenocarcinoma - small, solitary adenocarcinoma (3 cm), with a predominantly lepidic pattern and invasion of 5 mm or less in greatest dimension in any one focus. It is usually nonmucinous. Minimally invasive adenocarcinoma is, by definition, solitary and discrete.

## Minimally Invasive Adenocarcinoma



Travis. Arch Pathol Lab Med 2013;137:685-705

## Atypical Adenomatous Hyperplasia

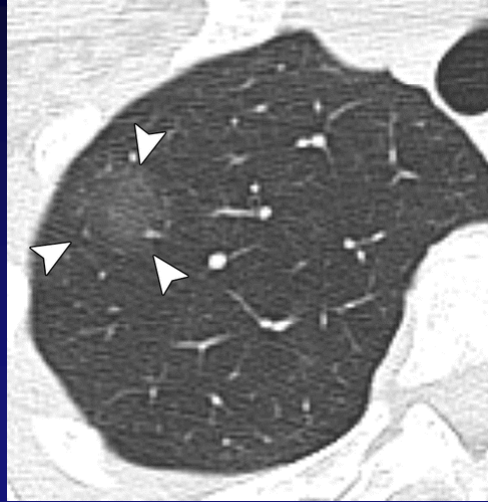
Typically has pure ground-glass attenuation and measures less than 1 cm.



Truong. RadioGraphics 2014;34:1658-79

## Adenocarcinoma In Situ

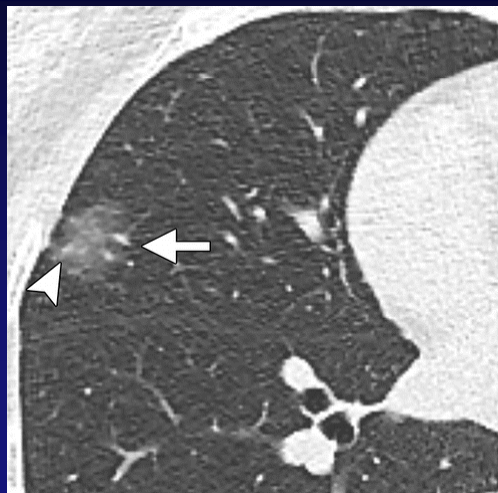
Typically has pure ground-glass attenuation and measures less than 3 cm.



Truong. RadioGraphics 2014;34;1658-79

## Minimally Invasive Adenocarcinoma

Ground-glass and solid components



Truong. RadioGraphics 2014;34;1658-79



## Correlation of Radiologic and Pathologic Findings

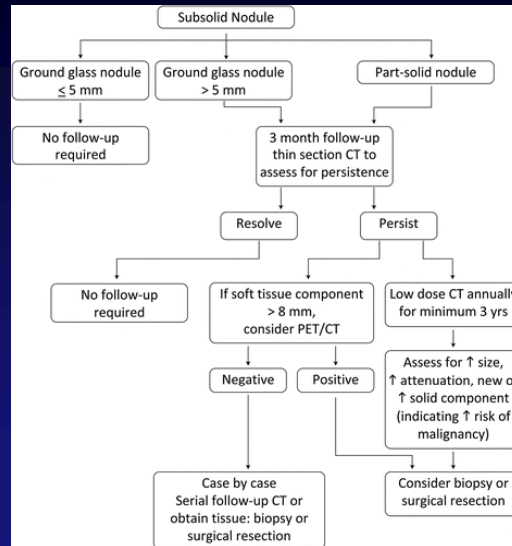
IASLC, ATS, ERS Classification	CT Features
Atypical Adenomatous Hyperplasia (AAH)	GGN – Ground-Glass Nodule
Adenocarcinoma <i>in situ</i>	GGN with a possible solid component
Minimally invasive adenocarcinoma	GGN, partially solid
Lepidic-predominant adenocarcinoma	Partly solid nodule, solid nodule
Invasive adenocarcinoma	Partly solid with a solid component, solid nodule

## Fleischner Society Recommendations for Management of Subsolid Pulmonary Nodules

- Ground Glass Nodule (GGN) < 5mm
  - Not CT follow-up, but obtain 1mm cuts to confirm that the nodule is purely ground glass
- Ground Glass Nodule > 5mm
  - Follow-up CT 3 months, if unchanged then annually x3 years
- Partially Solid Nodule
  - Follow-up at 3 months, if persistent and solid component < 5mm, then annual CT x 3yrs
  - If solid component > 5 mm, then biopsy or resection

Nadich. Radiology 2013; 266:304–17

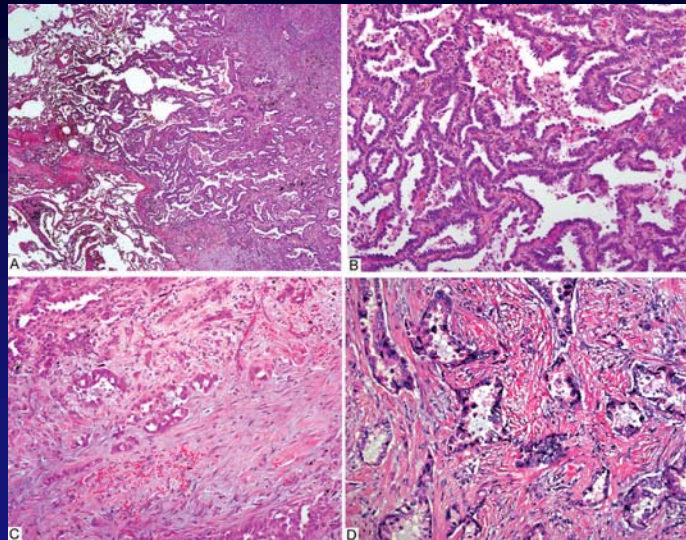
## Algorithm for Evaluation of a Subsolid Nodule



Patel. Chest 2013;143:84-6

## Invasive Adenocarcinoma

Present in at least 1 focus, measuring more than 5 mm in greatest dimension



Travis. Arch Pathol Lab Med 2013;137:685-705

# Invasive Adenocarcinoma

Lepidic-predominant adenocarcinoma (LPA) in its nonmucinous form. Necrosis may be present, and the focus of invasion of lymphatics and blood vessels is greater than 5 mm

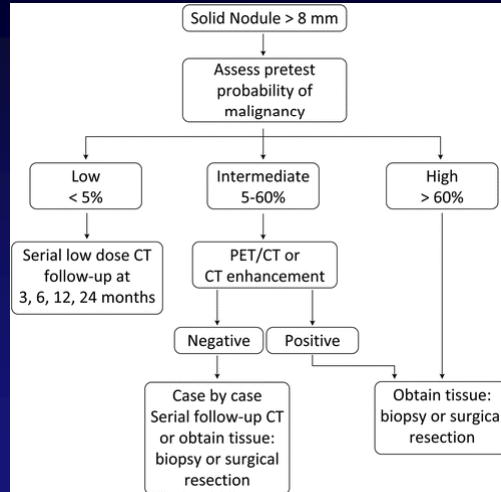


## Fleischner Society Recommendations for Follow-up of Solid Pulmonary Nodule

Size	Risk Factor	
	Low	High
≤ 4 mm	No follow-up	Follow-up 12 months
5-6 mm	Follow-up 12 months	Follow-up 6-12 months and 18-24 months
7-8 mm	Follow-up 6-12 months and 18-24 months	Follow-up at 3-6 months, 9-12 months, and 24 months
> 8 mm	Follow-up at 3, 9 and 24 months. Consider contrast enhanced CT, PET/CT or biopsy	Follow-up at 3, 9 and 24 months. Consider contrast enhanced CT, PET/CT or biopsy

**Nadich. Radiology 2013; 268:304-17** \* Little or no smoking history an other risk factors  
+ History of smoking or other exposure or risk factors

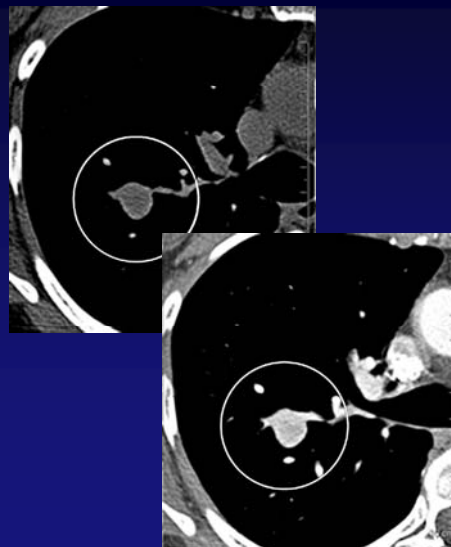
## Algorithm for Evaluation of a Solid Nodule



**Patel. Chest 2013;143:84-6**

## CT Characteristics of Malignancy

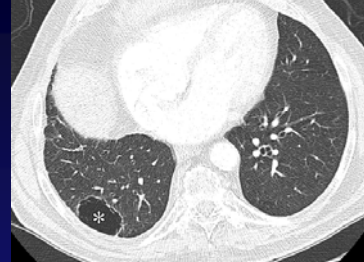
Carcinoid - images obtained before and after i.v contrast show the nodule has enhanced, with an increase in attenuation values of 109 HU.



**Truong. RadioGraphics 2014;34:1658-79**

## CT Characteristics of Malignancy

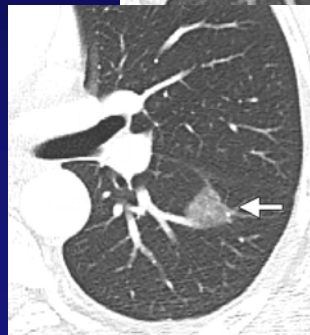
Lung Cancer - a cystic airspace (\*) in the right lower lobe. Follow-up CT image obtained 6 months later shows a new soft-tissue component (arrows) along the wall of the cystic airspace.



Truong. RadioGraphics 2014;34:1658-79

## CT Characteristics of Malignancy

Adenocarcinoma - Subsolid lesion that increased in size, which indicates an increased risk for malignancy. Follow-up 3 years later shows the increase in size to 1.8 cm.



## CT Characteristics of a Benign Process

Hamartoma - Contrast-enhanced CT shows a well-circumscribed left lower lobe nodule with low attenuation (-46 HU), a finding consistent with fat



Truong. RadioGraphics 2014;34;1658-79

## CT Characteristics of a Benign Process

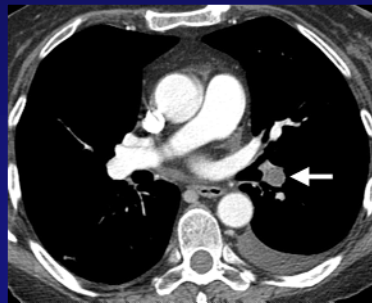
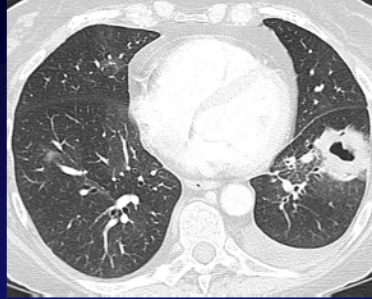
Granuloma - Benign pattern of calcification in a patient from the Ohio River valley. CT image shows a central, or "bull's-eye," area of calcification. The nodule is a result of Histoplasma capsulatum infection.



Truong. RadioGraphics 2014;34;1658-79

## CT Characteristics of a Benign Process

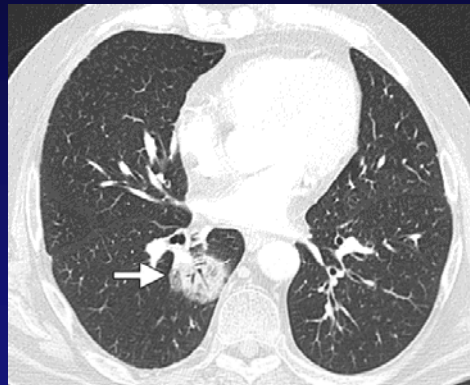
Pulmonary infarction - a thick-walled cavitary lesion in the left lower lobe and a small left pleural effusion. Contrast-enhanced CT image shows a pulmonary embolism in the left interlobar pulmonary artery



Truong. RadioGraphics 2014;34;1658-79

## CT Characteristics of a Benign Process

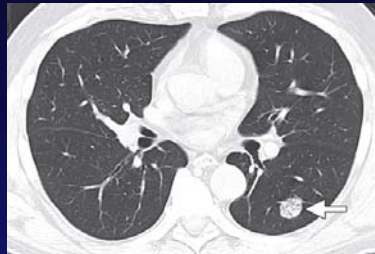
Fungal pneumonia - contrast-enhanced CT image shows a right-lower-lobe lesion and air-filled bronchi (the air bronchogram sign), findings consistent with pneumonia.



Truong. RadioGraphics 2014;34;1658-79

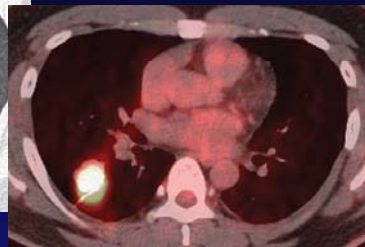
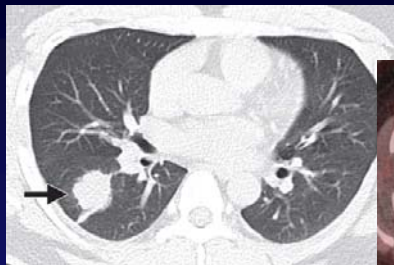
## PET/CT – False Negative

Adenocarcinoma -  
Slowly growing  
tumors will not be  
PET avid.

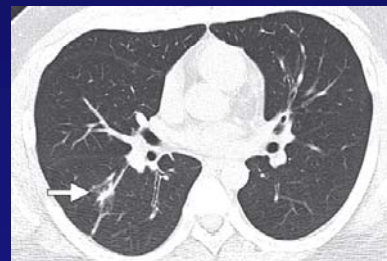


Truong. RadioGraphics 2014;34;1658-79

## PET CT – False Positive



CT and PET/CT images show a  
3-cm solid lesion in the right  
lower lobe with a maximum SUV  
of 16.7. Biopsy results revealed  
granulomatous inflammation.  
Follow-up CT image obtained 2  
months later shows regression of  
the lesion.





## Diagnostic Options

- PET/CT
  - Frequently below the detection threshold
  - Non avid nodules may represent slowly growing cancers
- Percutaneous biopsy
  - Often too small, too central
  - Specimen may not be sufficient to differentiate between invasive and non invasive lesions

## Diagnostic Options

- Navigational bronchoscopy
- Resection
  - Minimally invasive
  - Open
  - Frozen section will likely be unable to differentiate between invasive and minimally invasive tumors.

## Treatment of (very) Early Non-Small cell Lung Cancer

- Wedge/segmental resection are probably sufficient for the premalignant lesions (adenomatous hyperplasia, carcinoma *in situ*, minimally invasive adenocarcinoma)
- Lobectomy remains standard therapy for invasive cancers
  - Traditionally, less than lobectomy has been associated with increased local recurrence.
  - A randomized trial is currently accruing

## CALGB 140503

### A PHASE III RANDOMIZED TRIAL OF LOBECTOMY VERSUS SUBLOBAR RESECTION FOR SMALL ( $\leq$ 2 CM) PERIPHERAL NON-SMALL CELL LUNG CANCER

#### Patient Eligibility

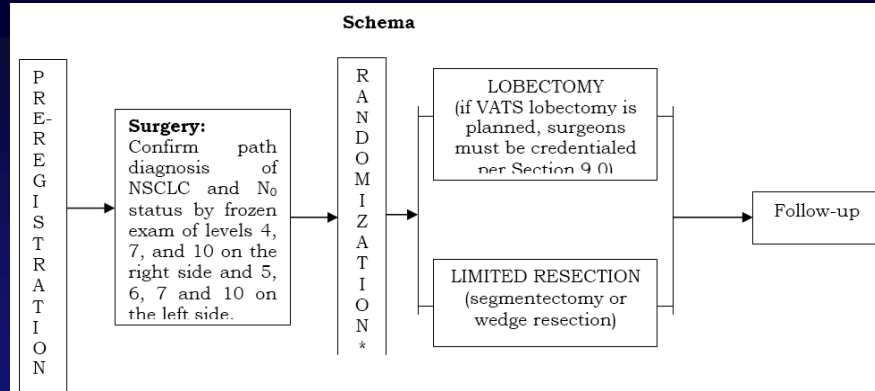
##### Pre-registration criteria

- Peripheral lung nodule  $\leq$  2 cm on CT and presumed to be lung cancer (see Sec 4.1.1)
- Tumor location suitable for either lobar or sublobar resection
- ECOG PS: 0-2
- No prior malignancy within 5 years (see Section 4.1.4)
- No prior chemotherapy or radiation therapy for this malignancy
- No evidence of locally advanced or metastatic disease
- Age  $\geq$  18 years

##### Intra-operative randomization criteria

- Histologic confirmation of NSCLC
- Confirmation of N<sub>0</sub> status (see Sec. 4.2.2)

## CALGB 140503



\* Randomization is done intra-operatively after determining patient eligibility. CALGB CRAs must be able to access the web-based CALGB registration system during surgery to obtain treatment assignment and inform the surgeon of the assignment at the site. Patients who are not randomized intraoperatively will not be considered "on-study" and should follow the instructions in Section 6.1.

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## Long-term Results of RTOG 0236: A Phase II Trial of SBRT in the Treatment of Patients with Medically Inoperable Stage I Non-small Cell Lung Cancer

R. Timmerman<sup>1</sup>, C. Hu<sup>2</sup>, J. Michalski<sup>3</sup>, W. Straube<sup>3</sup>, J. Galvin<sup>4</sup>, D. Johnstone<sup>5</sup>, J. Bradley<sup>3</sup>, R. Barriger<sup>6</sup>, A. Bezjak<sup>7</sup>, G. Videtic<sup>8</sup>, L. Nedzi<sup>1</sup>, M. Werner-Wasik<sup>4</sup>, Y. Chen<sup>9</sup>, R. Komaki<sup>10</sup>, H. Choy<sup>1</sup>

<sup>1</sup>Univ. Of Texas Southwestern Medical Ctr., Dallas, TX; <sup>2</sup>American College of Radiology, Philadelphia, PA; <sup>3</sup>Washington Univ., St. Louis, MO; <sup>4</sup>Th. Jefferson Hosp., Philadelphia, PA; <sup>5</sup>Medical College of Wisc., Milwaukee, WI; <sup>6</sup>Indiana Univ., Indpls., IN; <sup>7</sup>Princess Margaret Hosp., Toronto, ON; <sup>8</sup>Cleveland Clinic, Cleveland, OH; <sup>9</sup>Univ. of Rochester Medical Ctr., Rochester, NY; <sup>10</sup>MD Anderson Cancer Ctr., Houston, TX

ASTRO Annual Meeting  
September 15, 2014

## Eligibility

- Non-small cell lung cancer - biopsy proven
- T1, T2 ( $\leq 5$  cm) and T3 (chest wall only,  $\leq 5$  cm), N0, M0
- Medical problems preclude surgery (e.g. emphysema, heart disease, diabetes)
- No other planned therapy

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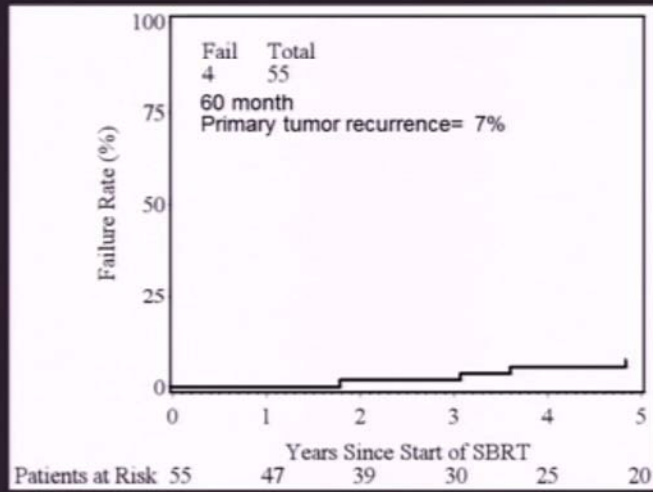
## Endpoints

- Primary endpoint 2-year primary tumor (in-field + marginal) recurrence
  - 2% of 55 evaluable patients (reported ASTRO 2009)
- Secondary endpoints disease free survival, overall survival, patterns of failure, and toxicity
  - 3 yr overall survival 56% (reported ASTRO 2009)
  - 3 yr local-regional (primary + intralobar + regional) failure 13% (reported JAMA 2010)
  - Disseminated failure 20% (reported ASTRO 2009)
- Grade  $\geq 3$  toxicity considered significant
  - 15 patients experienced such toxicity with no grade 5 toxicity (reported ASTRO 2009)

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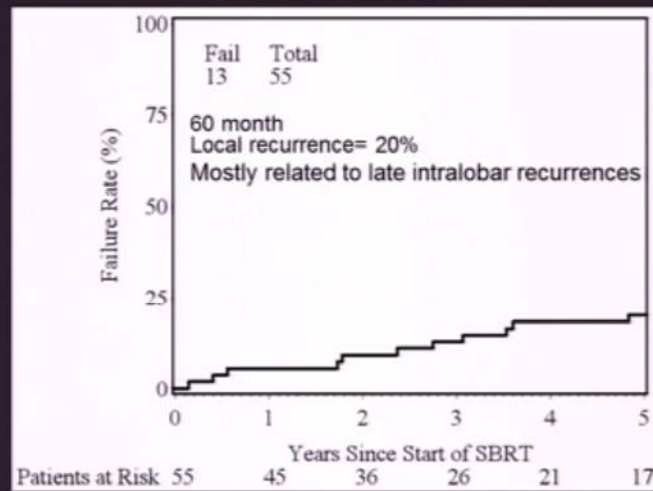
## Primary (In-field + Marginal) Tumor Recurrence

<1 cm from PTV



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## Local (primary + intralobar) Recurrence



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## Regional and Disseminated Recurrence

- 7 patients have a reported regional failure, out to 5+ years post SBRT
  - Only 2 patients in previous report
  - 5 year local-regional recurrence 38%
- 15 patients (31%) have experienced disseminated failure
  - 11 patient in previous report

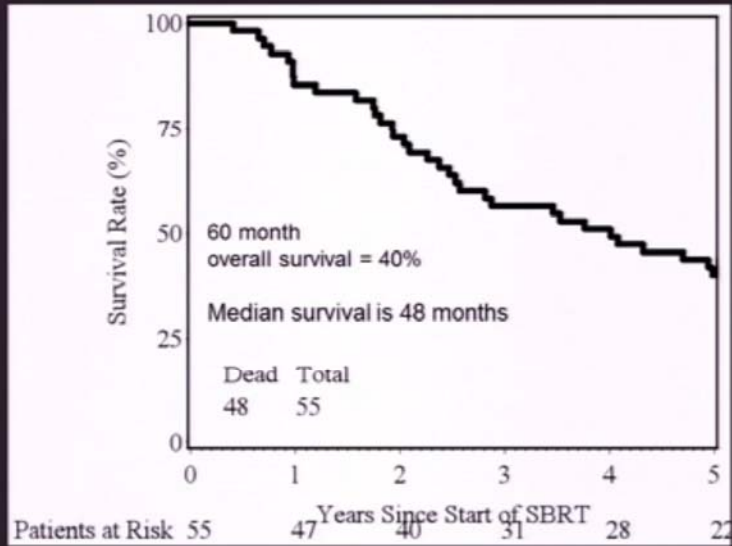
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## Disease Free Survival



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## Overall Survival



## Conclusions

- Primary tumor recurrence (treated area) remained very low at 5 years (7%) owing to the potent SBRT regimen
- Local-regional failure increased significantly, 38% at 5 years compared to 13% at 3 years, due to late failures (up to 6 years post SBRT) in mostly the involved lobe but also the hilum, and mediastinum (all untreated)  
*Recurrences? New primaries? Treatment Effects?*
- Severe toxicity remained relatively unchanged with longer follow-up
- Disease free and overall survival in this medically inoperable population at 5 years was 26% and 40%, respectively

## The Solitary Pulmonary Nodule in a Patient with Extrapulmonary Cancer

Type of Extrapulmonary Primary Malignancy	No. of Patients (n = 161)	No. of Patients with Metastases (n = 50)	No. of Patients with Primary Lung Cancers (n = 81)	No. of Patients with Benign Lesions (n = 30)
Head and neck squamous cell cancers	33	3 (9)	25 (76)	5 (15)
Lymphoma or leukemia	14	0 (0)	8 (57)	6 (43)
Carcinomas of the urinary bladder, breast, uterine cervix, biliary tree, esophagus, ovary, prostate, or stomach	45	8 (18)	26 (58)	11 (24)
Carcinomas of the salivary glands, adrenal gland, colon, parotid gland, kidney, thyroid gland, thymus, or uterus	31	16 (52)	13 (42)	2 (6)
Melanoma, sarcoma, or testicular carcinoma	38	23 (60)	9 (24)	6 (16)

Numbers in parentheses are percentages.

Quint. Radiology 2000;217:257-61

## The National Lung Screening Trial

- Conducted by NCI Division of Cancer Prevention and American College of Radiology (ACRIN)
- Randomized between annual chest x-ray or low dose CT x 3 years
- Two phases
  - Screening Feasibility Phase (2000)
  - Actual trial enrollment (2002-2004)
- No follow-up guidelines for abnormal findings

NLST. NEJM 2011;365:395-409



## NLST: Eligibility and Exclusion Criteria

- Eligibility
  - Age 55-74
  - > 30 pack years
  - Currently smoking
  - Former smokers: stopped within previous 15 years
- Exclusion
  - History of lung cancer
  - Any cancer within five years\*
  - Previous lung surgery
  - Need for home oxygen
  - Unexplained weight loss > 15 lbs in prior 12 months
  - Hemoptysis
  - Chest CT within prior 18 months

\*Other than: nonmelanoma skin cancer or carcinoma in situ (except transitional cell carcinoma in situ or bladder carcinoma in situ)

NLST. NEJM 2011;365:395-409

## NLST: CT Interpretation Categories

Negative or minor abnormality: not suspicious for lung cancer

Positive: suspicious for lung cancer

No findings or minor findings not suspicious for lung cancer, such as morphologically benign nodules or noncalcified nodules < 4 mm

Noncalcified nodule > 4mm, lung consolidation, nodule enlargement, nodules with suspicious changes in attenuation

NLST. NEJM 2011;365:395-409

## The National Lung Screening Trial

- N=53,456 (enrolled in two years!!)
- Last screening round 2007
- 90% power to detect a 21% reduction in lung cancer mortality
- Follow-up data collected until 12/09
- X-rays read locally by NLST trained/approved radiologists

NLST. NEJM 2011;365:395-409

## The National Lung Screening Trial

- Primary endpoint – lung cancer mortality
- Secondary endpoints
  - incidence and stage across arms and screening centers
  - sensitivity, specificity, positive and negative predictive values

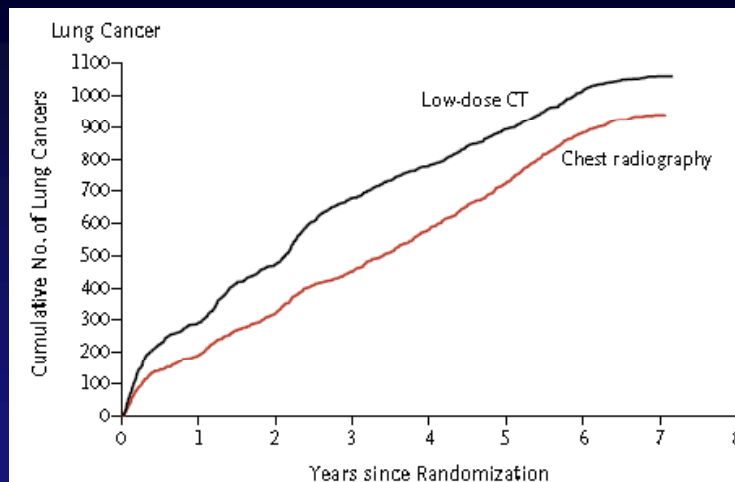
NLST. NEJM 2011;365:395-409

## NLST: Results

- 20.3% reduction in lung cancer mortality in patients screened with CT relative to those screened with chest X-ray
- 7% decrease in all cause mortality in patients screened with CT relative to those screened with chest X-ray
- 24.2% of CT scans were classified as positive
- 96.4% false positive in the CT arm

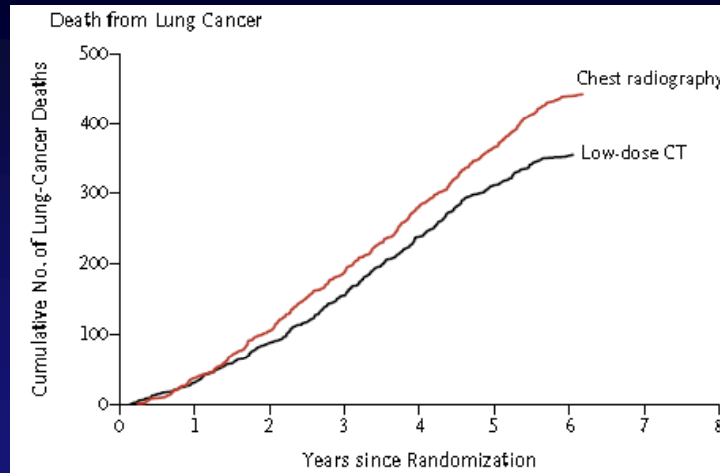
NLST. NEJM 2011;365:395-409

## The National Lung Screening Trial



NLST. NEJM 2011;365:395-409

# The National Lung Screening Trial



NLST. NEJM 2011;365:395-409

What % of the U.S. population and incident lung cancers would be covered by applying the NLST eligibility criteria?

- Estimated total number of lung cancers from SEER data and the U.S. census
- Estimated the proportion of the population in smoking categories with the 2010 National Health Interview Survey
- Calculated Relative Risk from statistical models

Pinsky and Berg. J Med Screen 2012;19:154-6

Smoking category		55-74	50-74	55-79	50-79
A. Current or quit within 15 years, 30 + pack years*	% of cancers	26.7	29.1	32.9	35.3
	% of population over 40	6.2	8.3	6.8	8.9
	Incidence rate (per 10 <sup>5</sup> PY)	579	470	655	535
B. 30 + pack years (any quit status)	% of cancers	32.5	35.0	43.8	46.3
	% of population over 40	8.3	10.7	9.7	12.1
	Incidence rate (per 10 <sup>5</sup> PY)	537	449	616	523
C. Current or quit within 15 years (any pack years)	% of cancers	36.6	40.9	44.5	48.8
	% of population over 40	11.4	17.0	12.3	17.9
	Incidence rate (per 10 <sup>5</sup> PY)	436	326	492	371
D. Ever smoker	% of cancers	47.9	52.6	63.5	68.2
	% of population over 40	19.4	27.1	22.3	30.0
	Incidence rate (per 10 <sup>5</sup> PY)	332	262	384	307

- Screening the NLST group will decrease all NSCLC mortality by 5% (20% of 26.7% of all lung cancers)
- Except for increasing the age range to 55-79, all other groups would require screening more patients to identify the same number of cancers

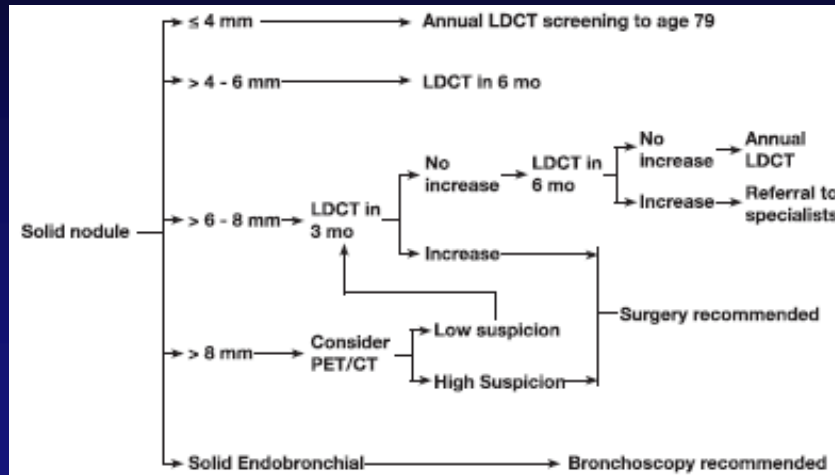
Pinsky and Berg, J Med Screen 2012;19:154-6

## Defining Screen Positivity – Perhaps Three Dimensions are Better than One

- NLST
  - > 4mm greatest diameter - positive
  - 24% of all CTs were positive
- NELSON trial (Dutch Belgian randomised lung cancer screening trial) NEDerlands Leuven Longkanker Screenings Onderzoek
  - > 500mm<sup>3</sup> - positive
  - 50-500mm<sup>3</sup> – indeterminate which were followed with a repeat CT in 3 months. Volume increase of >25% was utilized to characterize as positive or negative
  - 2.6% of all CTs were positive, sensitivity 94.6%, negative predictive value 99.9%

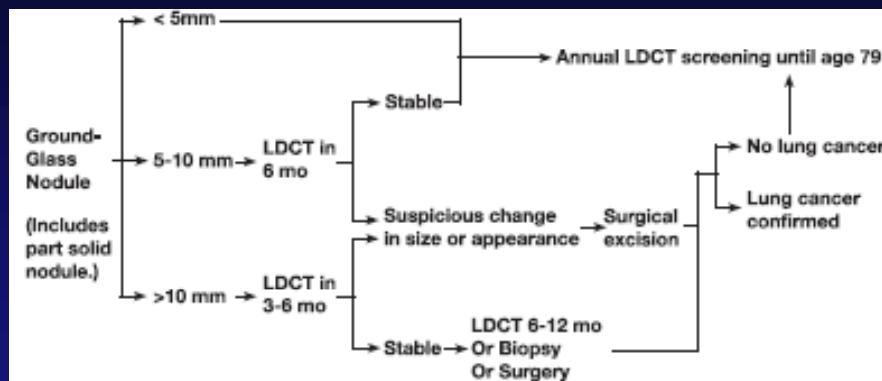
Field et al. J Thorac Oncol 2012;7:10-9

## Recommendations of The American Association for Thoracic Surgery (AATS) Task Force for Lung Cancer Screening and Surveillance



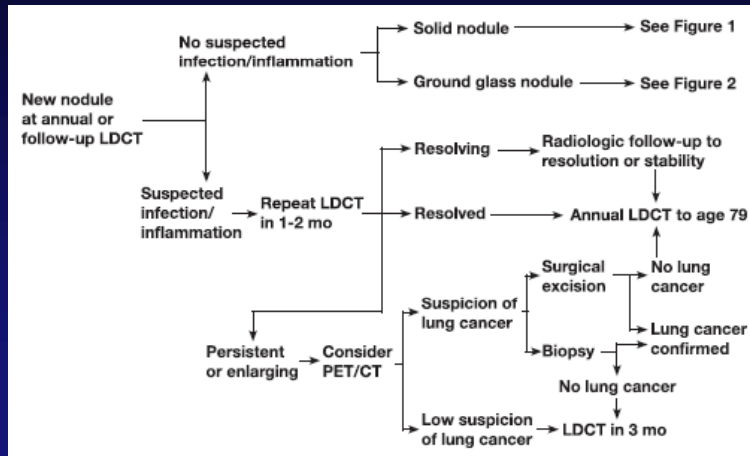
Jacobson et al. J Thorac Cardiovasc Surg 2012;144:25-32)

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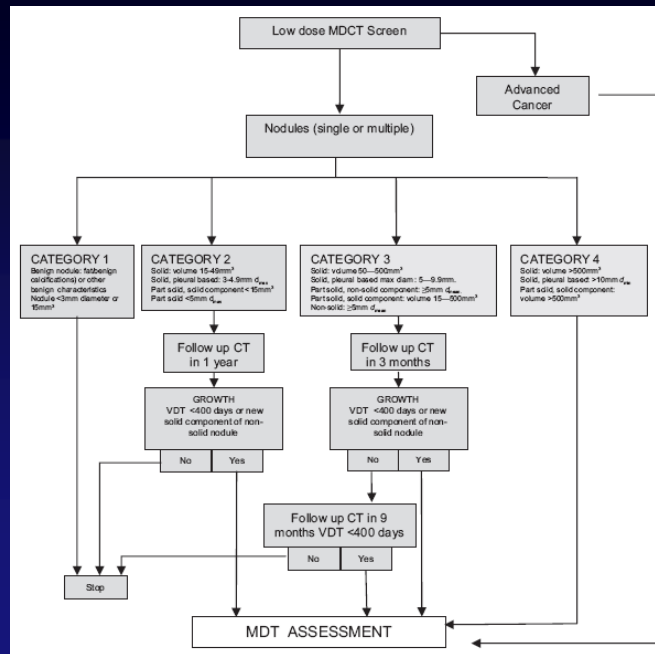
Jacobson et al. J Thorac Cardiovasc Surg 2012;144:25-32)

## UK Lung Screen (UKLS) nodule management: modeling of a single screen randomised controlled trial of low-dose CT screening for lung cancer

	Solid	Non-solid or part solid
Category 1	Nodules containing fat or with a benign pattern of calcification are considered benign. Nodules <math><15\text{ mm}^3</math> or if pleural or juxta pleural $\leq 3\text{ mm}</math>$	
Category 2	Intraparenchymal nodules with a volume of $15\text{--}49\text{ mm}^3</math>. Pleural or juxtaleural nodules with a maximal diameter of 3.1\text{--}4.9\text{ mm}</math>.$	Nodules with a maximal non-solid component diameter $< 5\text{ mm}</math>. Where there is a solid component, the component volume is < 15\text{ mm}^3</math>$
Category 3	Intraparenchymal nodules with a volume of $50\text{--}500\text{ mm}^3</math>. Pleural or juxtaleural nodules with a maximal diameter of 5\text{--}9.9\text{ mm}</math>.$	Nodules with a maximal non-solid component diameter of $> 5\text{ mm}</math>. Where there is a solid component, the component volume is 15\text{--}500\text{ mm}^3</math>$
Category 4	Intraparenchymal nodules with a volume $> 500\text{ mm}^3</math>. Pleural or juxtaleural nodules with a maximal diameter of \geq 10\text{ mm}</math>.$	Nodules with a solid component with a volume $> 500\text{ mm}^3</math>$

Baldwin et al. Thorax 2011;66:308-313.)

## UK Lung Screen (UKLS) nodule management



Baldwin et al. Thorax 2011;66:308-13

## Factors that Increase the Risk of Lung Cancer

- Age
- Gender
- Cigarette smoking history and duration
- Second hand smoke in never-smokers
- Bronchitis, emphysema (FEV1 <70%), pneumonia
- Asbestos exposure
- Family history of lung cancer
- Low socioeconomic status
- Low BMI

Raji et al. Ann Intern Med;157:242-50 and Temmermagi et al. JNCI 2011;103:1058-68



## Factors that Increase the Risk of Lung Cancer

- Snip markers for COPD/Lung Cancer
  - Young et al. *Frontiers Genet* 2012;3:1-7
- Serum proteomics
  - Pecot et al. *Cancer Epidemiol Biomarkers Prev* 2012;21:786-92
- Plasma DNA – aberrant methylation of tumor suppressor genes
  - Ostrow et al. *Clin Cancer Res* 2010;16:3463-72
- Abnormal sputum cytology
  - Giordano and Bagella. *J Cell Physiol.* 2013 May;228:945-51

Young et al. *Frontiers Genet* 2012;3:1-7

## Toenail Nicotine Level as a Novel Biomarker for Lung Cancer

- Health Professional Follow-up Study initiated 1986
  - n=51,529
  - Predominantly white males ages 40-75 years
  - 1987 – 33,737 sent toenail clippings
  - 210 cases with lung cancer and 630 matched controls for total 840 patients
  - Toenail nicotine has a long half-life
  - Toenails grow slowly 1cm/year

Al-Delaimy WK, Willet WC. *Am J Epidemiol* 2011;173(7):822-28

## Toenail Nicotine Level as a Novel Biomarker for Lung Cancer

	Toenail Nicotine Quintile, ng/mg				
	1	2	3	4	5
No. of men	179	164	163	166	168
Median toenail nicotine, ng/mg	0.04	0.07	0.10	0.20	1.28
Age in years, mean (SD)	62.8 (8.8)	62.7 (8.0)	63.8 (7.5)	63.8 (7.1)	60.7 (8.0)
Physical activity, METs	19.2	21.0	18.8	19.6	15.0
Body mass index, kg/m <sup>2</sup>	25.0	25.0	25.2	25.5	24.7
Pack-years of smoking, no.	11.2	12.7	15.8	19.3	37.3
Smoking status, %					
Never smoker	29.2	24.0	23.6	17.5	5.7
Past smoker	21.6	21.3	21.5	23.0	12.6
Current smoker	0.0	1.2	1.1	12.6	85.2

Abbreviations: MET, metabolic equivalent task-hour; SD, standard deviation.

Al-Delaimy WK, Willet WC. Am J Epidemiol 2011;173(7):822-28

## Toenail Nicotine Level as a Novel Biomarker for Lung Cancer

Variable	Multivariate Analysis					
	Univariate Analysis		Model 1 <sup>a</sup>			
	RR	95% CI	RR	95% CI	RR	95% CI
Pack-years of smoking						
0 (19 cases)	1.00				1.00	
1–9 (12 cases)	2.18	0.98, 4.84			1.92	0.83, 4.44
10–19 (9 cases)	1.46	0.62, 3.47			1.36	0.55, 3.34
20–29 (30 cases)	5.44	2.82, 10.51			4.66	2.35, 9.24
30–39 (35 cases)	10.39	5.28, 20.44			7.68	3.75, 15.73
≥40 (105 cases)	26.05	13.90, 48.81			15.80	8.06, 30.97
<i>P</i> for trend		<0.0001				<0.0001
Nicotine quintile						
1 (26 cases)	1.00		1.00		1.00	
2 (21 cases)	1.02	0.52, 1.99	0.82	0.40, 1.69	0.83	0.38, 1.82
3 (26 cases)	1.43	0.74, 2.75	1.23	0.61, 2.47	1.09	0.51, 2.34
4 (40 cases)	2.10	1.12, 3.93	1.34	0.68, 2.67	1.30	0.62, 2.73
5 (97 cases)	10.50	5.61, 19.64	3.16	1.49, 6.73	3.57	1.73, 7.37
<i>P</i> for trend		<0.0001		0.0004		<0.0001

Al-Delaimy WK, Willet WC. Am J Epidemiol 2011;173(7):822-28

## Conclusions

- Growing nodules should be removed/treated
- Wedge resection/segmental resection sufficient for pre invasive cancers
- Screening an at risk population with low dose annual CT scans reduces lung cancer mortality by 20%