Screening Populations: COPD or Lung Cancer or Both? Risk in High-Risk Populations

C. Matthew Kinsey MD, MPH
Director, Interventional Pulmonary
Assistant Professor
University of Vermont

Vermont Cancer Center
University of Vermont • Fletcher Allen Health Care

VERMONT LUNG CENTER

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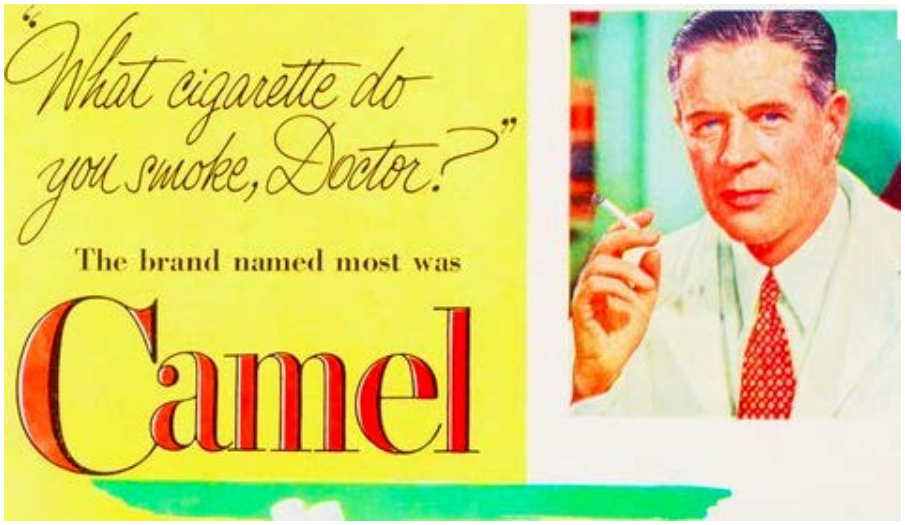
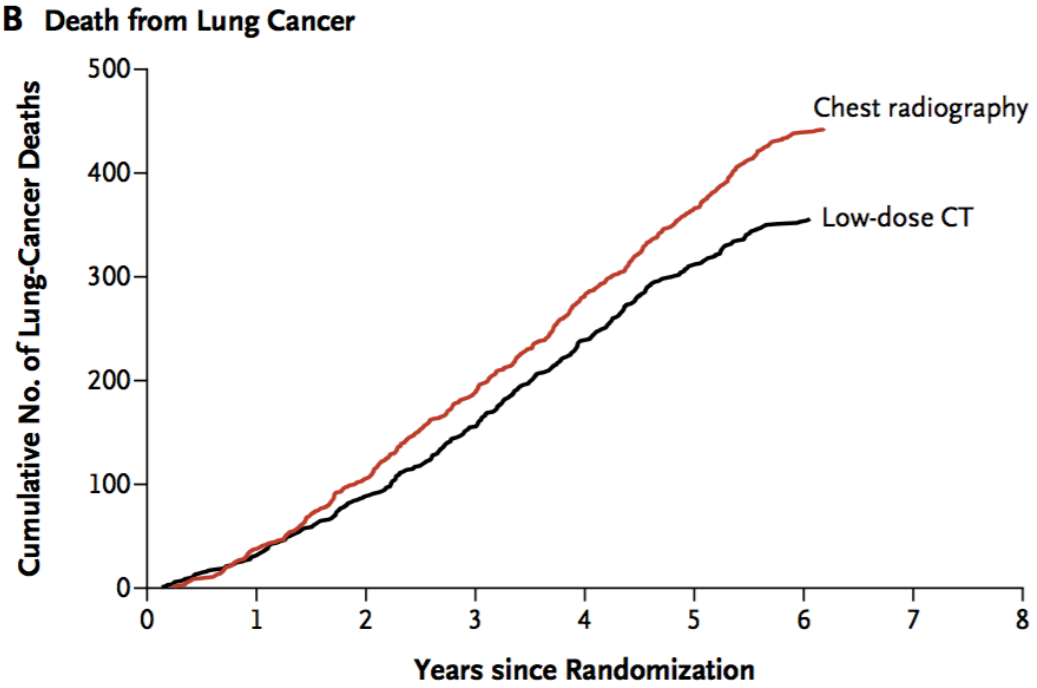


Outline:

1) Risks in a screening population

2) COPD and emphysema as risks for lung cancer

3) Non-nodular CT features as risks for lung cancer death



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Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

Aged 55-74, 30 pk-yr (quit <15 yr prior), annual CT x 3 years

≥ 4mm considered positive

Table 7. Cause of Death on the Death Certificate, According to Screening Group.*

Cause of Death	Low-Dose CT Group	Radiography Group	Total
	number/total number (percent)		
Neoplasm of bronchus and lung†	427/1865 (22.9)	503/1991 (25.3)	930/3856 (24.1)
Other neoplasm	416/1865 (22.3)	442/1991 (22.2)	858/3856 (22.3)
Cardiovascular illness	486/1865 (26.1)	470/1991 (23.6)	956/3856 (24.8)
Respiratory illness	175/1865 (9.4)	226/1991 (11.4)	401/3856 (10.4)
Complications of medical or surgical care	12/1865 (0.6)	7/1991 (0.4)	19/3856 (0.5)
Other	349/1865 (18.7)	343/1991 (17.2)	692/3856 (17.9)

Risks: Benefits and harms of CT screening

20% relative risk reduction, 0.33% absolute risk reduction

649 cancers (3.6% of positive tests)

NNS: 320, NNH: 52 (potentially avoidable invasive procedure)

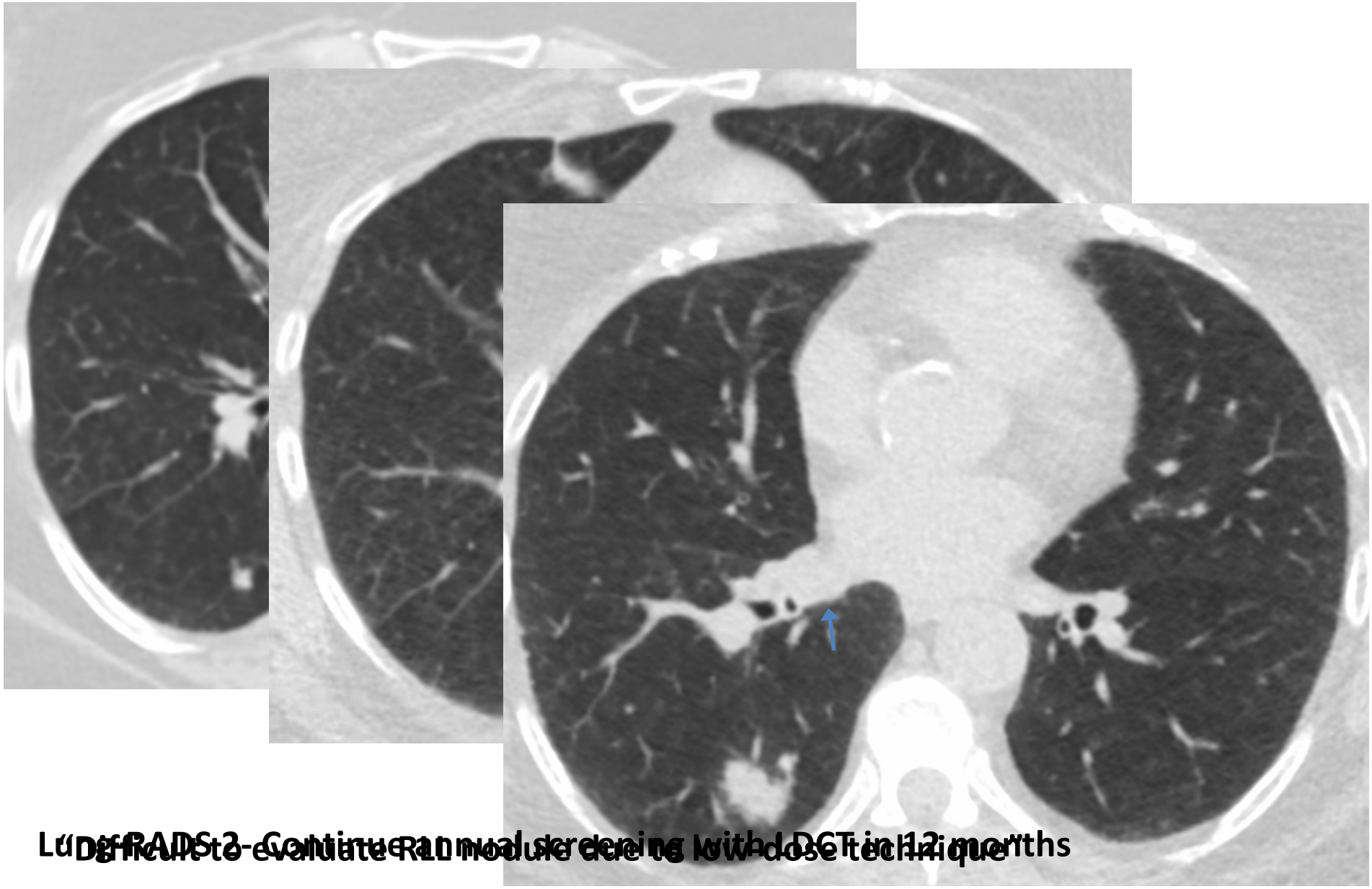
New Definition (LungRADS): ≥ 6mm considered positive
Sensitivity decreases from 94% to 85%

However even at the ≥4mm cutoff, 29% of lung cancer deaths occurred in non-screen detected cases*

Yip, R., Henschke, C. I., Yankelevitz, D. F., & Smith, J. P. *Radiology*, *273*(2), 591–596. (2014)
Pinsky, P. F., Gierada, D. S., et al. *Annals of Internal Medicine*, *162*(7), 485–491. (2015)

** based on years T0-T2, NLST-163 PI: Kinsey*

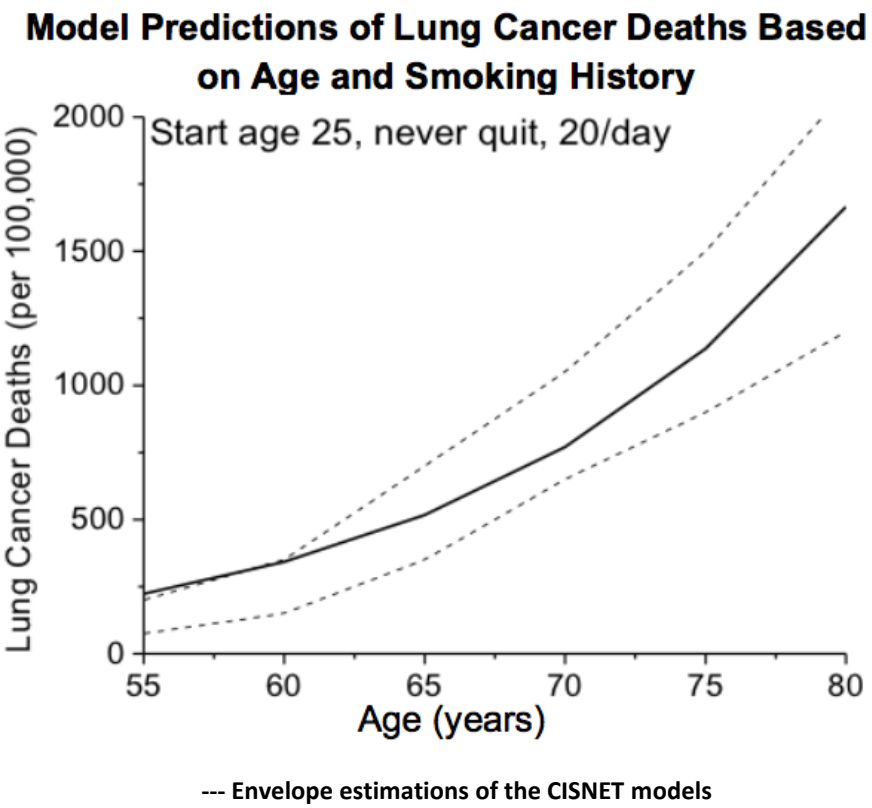
A low-risk nodule…



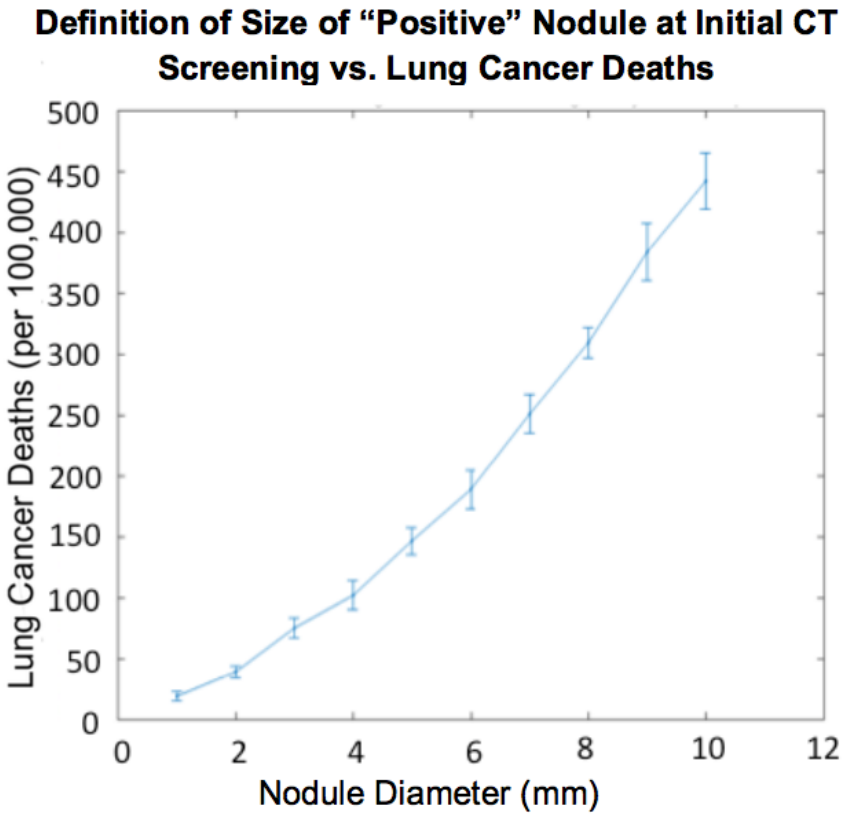
Lung-RADS 2- Continue annual screening with LDCT in 12 months

Difficult to evaluate RLL nodule dere to low-dose technique

Risk: Small changes may threaten the screening benefit



--- Envelope estimations of the CISNET models

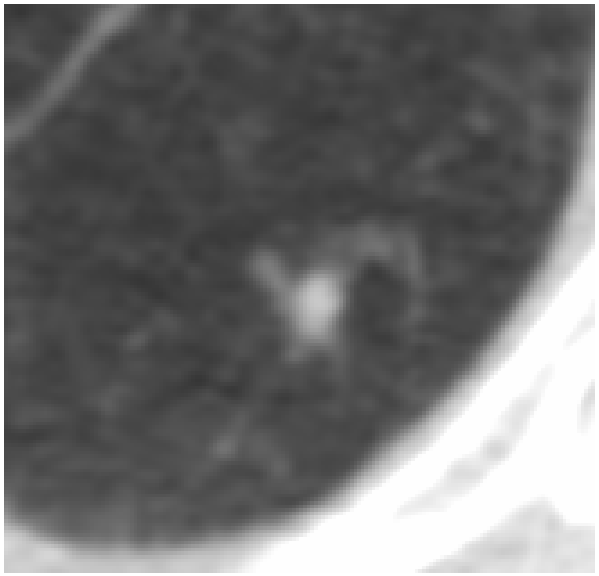


Monte-Carlo simulation may be used to estimate changes in lung cancer mortality in the setting of lung cancer screening.

An upper bound estimation argues that increasing nodule size alone may result in a small increase in LC deaths

Kinsey et al. *PlosOne*. under review

Prevent Cancer Foundation Executive Summary 2015: "With lung cancer screening however, there are new opportunities to have a greater impact with such efforts, as the information obtained with a lung CT contains three-dimensional information that is much more informative than the usual two-dimensional information obtained with standard mammography."



Moving forward can we use features other than those of the nodule to help define lung cancer risk?

COPD: Reduced FEV1 is associated with lung cancer

Table 3 Relative risk (with 95% confidence interval) of lung cancer for men and women in different quintiles of lung function

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Men					
Hole[10]	2.53 (1.68 to 3.82)	1.93 (1.27 to 2.94)	1.80 (1.17 to 2.77)	1.36 (0.86 to 2.16)	1.00
Kuller[11]	3.56 (1.02 to 12.43)	2.44 (1.17 to 5.05)	2.80 (1.32 to 5.93)	0.50 (0.11 to 2.34)	1.00
Mannino[12]	3.16 (1.20 to 8.33)	1.03 (0.35 to 3.06)	1.11 (0.35 to 3.46)	0.94 (0.29 to 3.10)	1.00
Van Den Eeden[13]	1.86 (1.32 to 2.64)	1.60 (1.35 to 1.90)	1.45 (1.20 to 1.75)	1.34 (1.04 to 1.72)	1.00
Pooled summary	2.23 (1.73 to 2.86)	1.67 (1.42 to 1.93)	1.54 (1.30 to 1.82)	1.30 (1.05 to 1.62)	1.00
Women					
Hole[10]	4.39 (1.86 to 10.38)	4.14 (1.73 to 9.87)	4.01 (1.68 to 9.58)	3.63 (1.51 to 8.76)	1.00
Mannino[12]	5.99 (0.75 to 47.94)	8.58 (1.09 to 67.36)	8.76 (1.09 to 70.11)	1.08 (0.07 to 17.29)	1.00
Van Den Eeden[13]	1.95 (0.32 to 11.70)	1.45 (0.27 to 7.69)	1.80 (0.52 to 6.30)	1.55 (0.41 to 5.81)	1.00
Pooled summary	3.97 (1.93 to 8.25)	3.71 (1.80 to 7.69)	3.46 (1.75 to 6.75)	2.64 (1.30 to 5.31)	1.00
Pooled summary for men and women	2.36 (1.88 to 3.00)	1.72 (1.48 to 1.99)	1.62 (1.38 to 1.90)	1.38 (1.13 to 1.70)	1.00

All data were merged using a fixed effects model because there was no significant heterogeneity in data across the studies ($p>0.10$).

10-40% of patients with CT emphysema have normal lung function, making emphysema a potentially more sensitive biomarker for LC

Wasswa-Kintu, S. et al. *Thorax*, *60*(7), 570–575. (2005)
Schroeder, J. D., et al *Am J Roentgenol*, *201*(3), W460–70 . (2013)
Regan EA, et al. JAMA Intern Med. Sep;175(9):1539-49.(2015)

Quantitative emphysema (%LAA) is only weakly associated with lung cancer

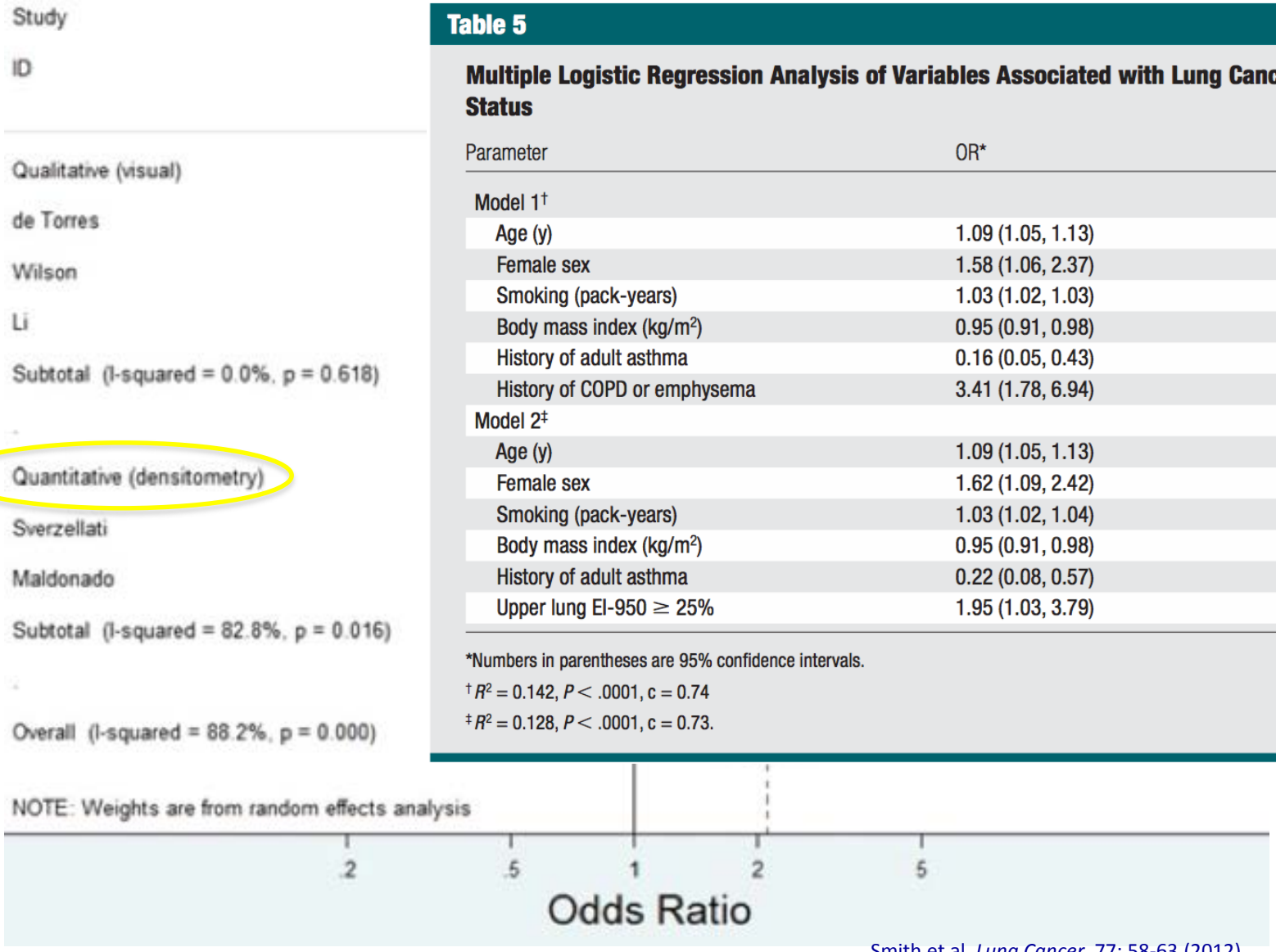


Table 5

Multiple Logistic Regression Analysis of Variables Associated with Lung Cancer Status

Parameter	OR*	*P* Value
Model 1†		
Age (y)	1.09 (1.05, 1.13)	6.86E-6
Female sex	1.58 (1.06, 2.37)	.0244
Smoking (pack-years)	1.03 (1.02, 1.03)	5.28E-8
Body mass index (kg/m^2)	0.95 (0.91, 0.98)	.0059
History of adult asthma	0.16 (0.05, 0.43)	.0005
History of COPD or emphysema	3.41 (1.78, 6.94)	.0004
Model 2‡		
Age (y)	1.09 (1.05, 1.13)	.00001
Female sex	1.62 (1.09, 2.42)	.017
Smoking (pack-years)	1.03 (1.02, 1.04)	1.46E-8
Body mass index (kg/m^2)	0.95 (0.91, 0.98)	.0040
History of adult asthma	0.22 (0.08, 0.57)	.0030
Upper lung EI-950 ≥ 25%	1.95 (1.03, 3.79)	.0438

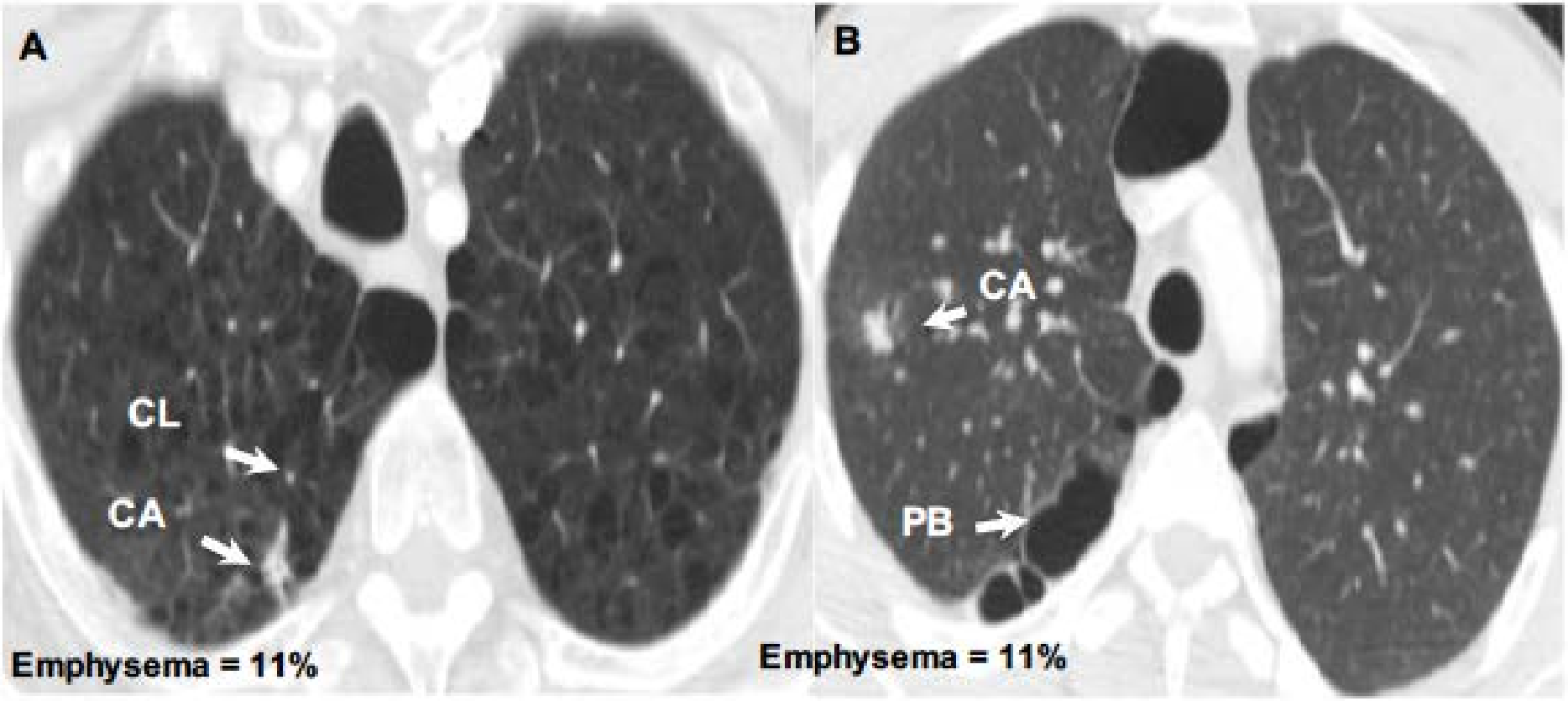
*Numbers in parentheses are 95% confidence intervals.

† $R^2 = 0.142$, $P < .0001$, c = 0.74

‡ $R^2 = 0.128$, $P < .0001$, c = 0.73.

Smith et al. *Lung Cancer*. 77; 58-63 (2012)
Gierada et al. Radiology. 261 (3): 950-9 (2011)

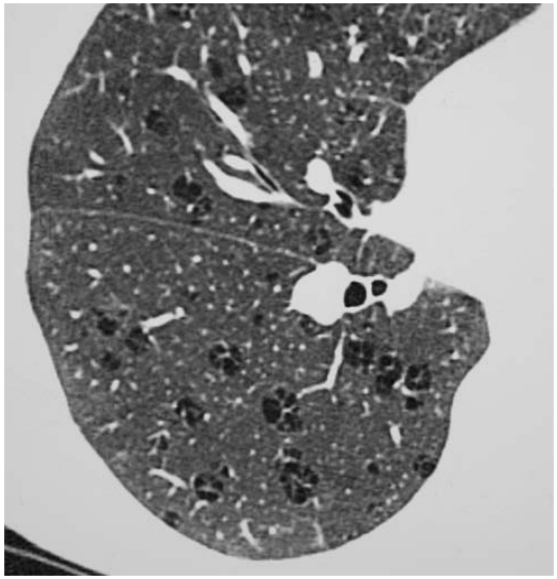
Emphysema is emphysema, right?



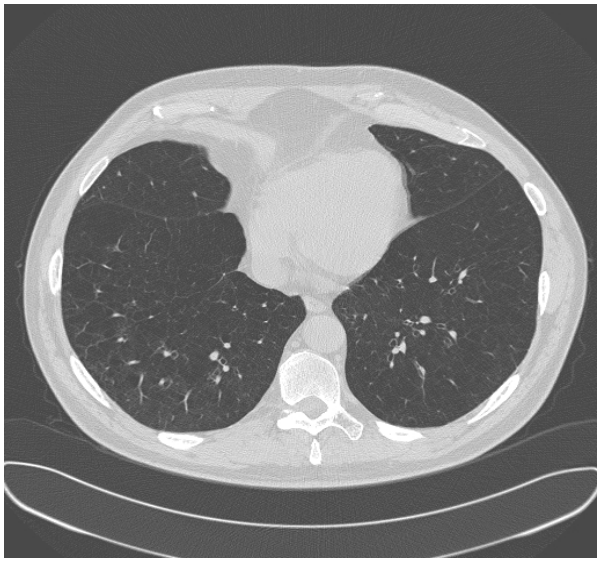
Densitometric emphysema does not capture all potentially important information

Patterns of Emphysema in COPD

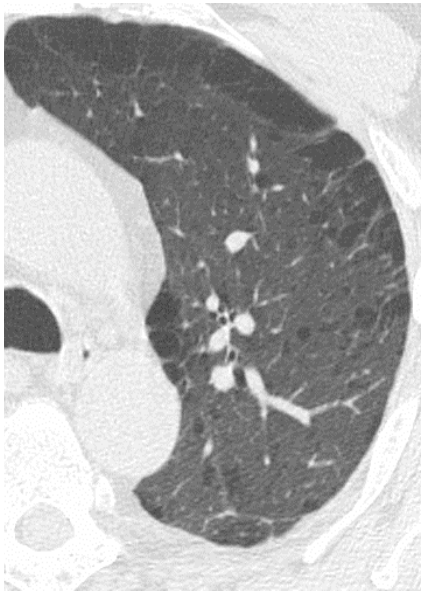
Centrilobular Emphysema



Panlobular Emphysema



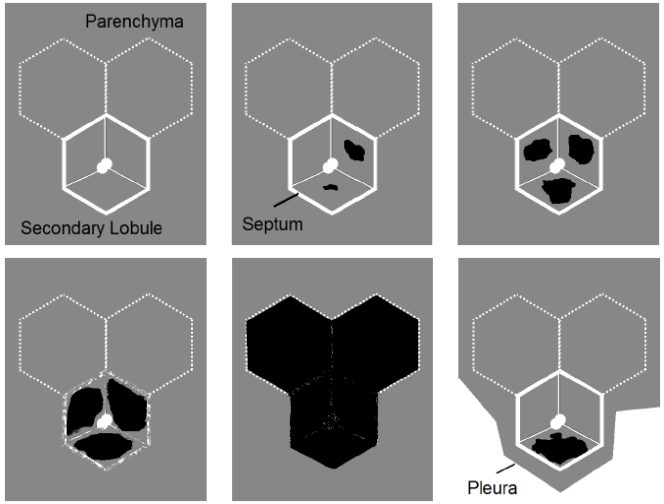
Paraseptal Emphysema



Courtesy of Raul San José Estépar

Radiographic Classification

Secondary Lobule Schematic Description



Non emphysema

Mild centrilobular

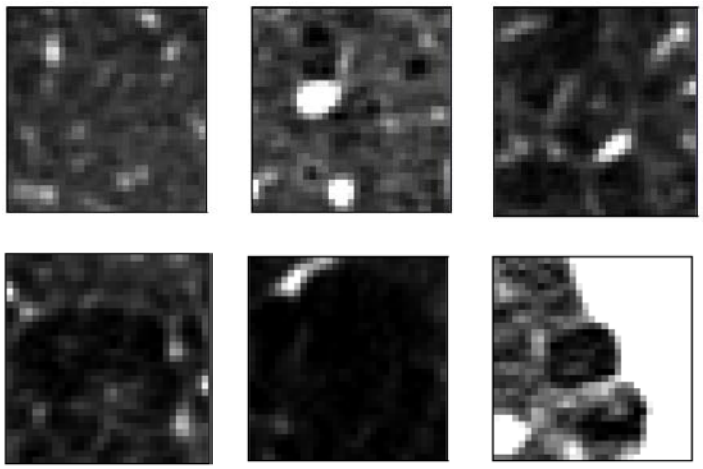
Moderate centrilobular

Severe centrilobular

Panlobular

Paraseptal

Radiologic expression in *HRCT*

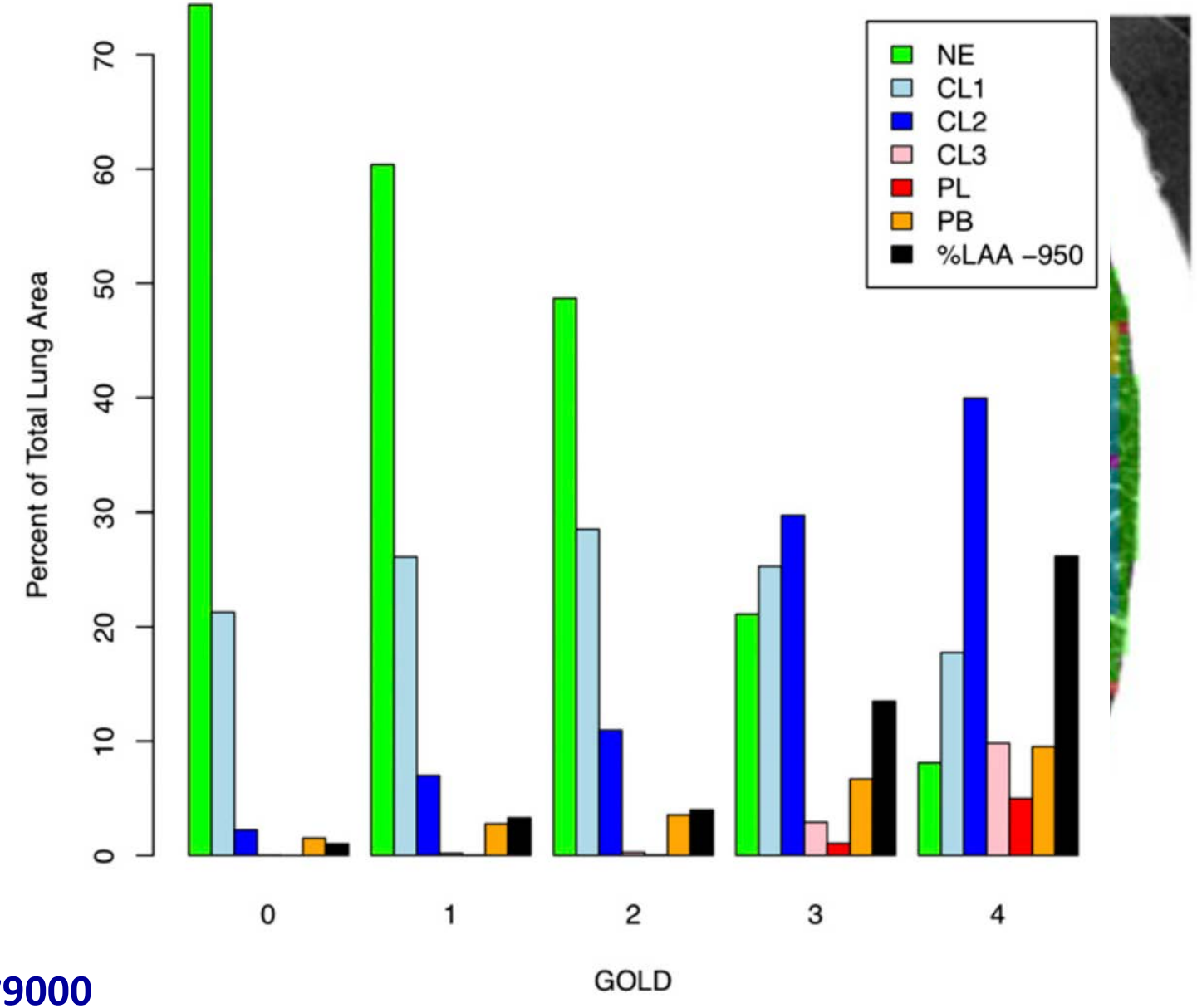


~ 2.5 cm

Incorporate spatial statistical structure (texture) of low density regions.

Courtesy of Raul San José Estépar

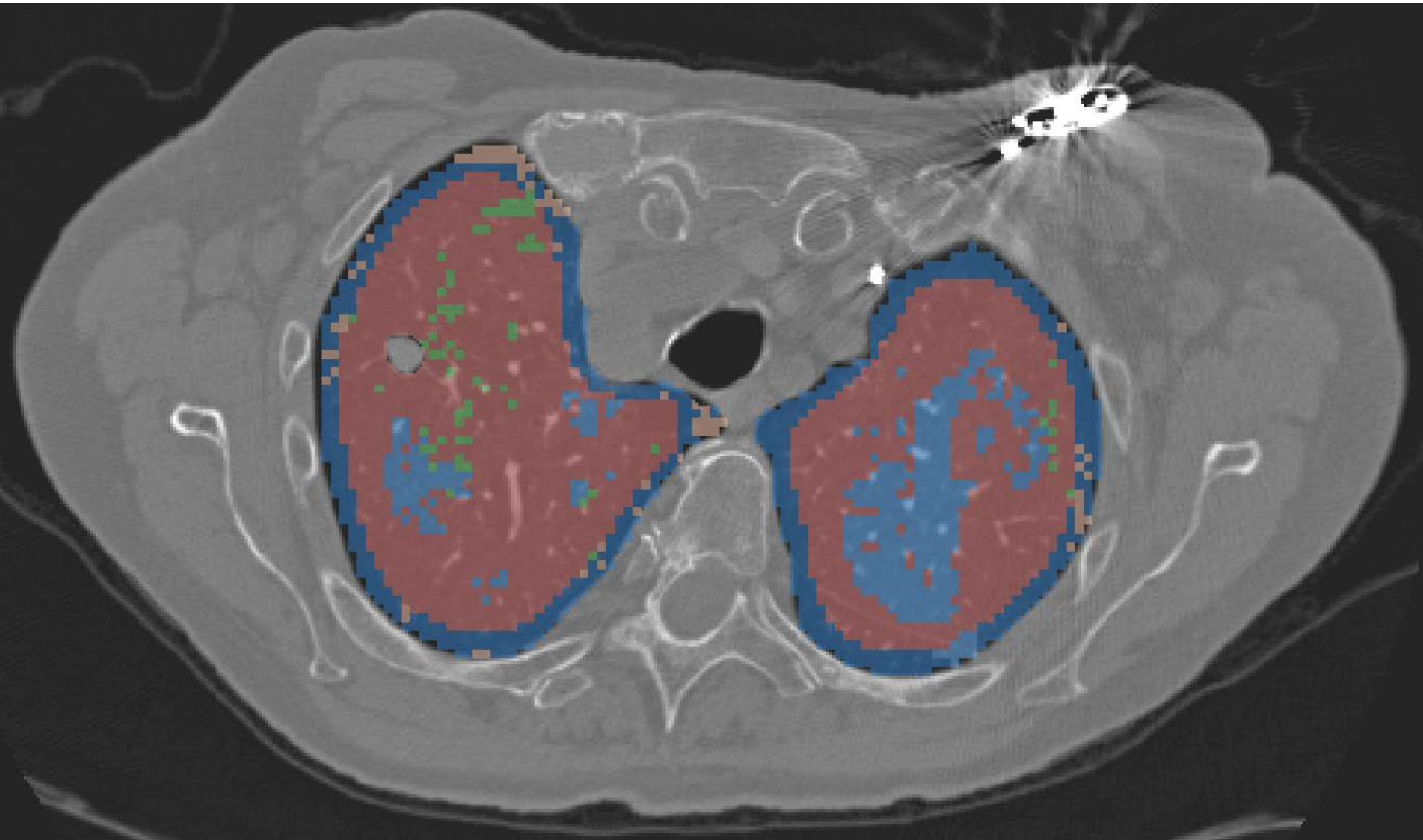
Emphysema morphology partially determines physiology



N= ~9000

Castaldi, P. J., San Jose Estepar R, et al. (2013). *American Journal of Respiratory and Critical Care Medicine*, *188*(9), 1083–1090.

Is a higher proportion of a particular emphysema morphology associated with a risk for lung cancer?



Moderate centrilobular emphysema is associated with a risk for lung cancer

8355 controls vs. 275 cases

Lung Parenchymal Feature	OR	CI	P value
%LAA -950 (density threshold alone)	1.01	[0.99, 1.02]	0.146
Mild centrilobular (CL1)	0.26	[0.17, 1.61]	0.263
Moderate centrilobular (CL2)	**2.41**	**[1.09, 5.32]**	**0.029**
Severe centrilobular (CL3)	6.12	[0.97, 38.6]	0.054
Panlobular (PL)	4.99	[0.23, 108.8]	0.306
Pleural-based (PB)	13.4	[0.00, 1137]	0.713

Each model includes one of the above lung parenchymal features and is adjusted for age, gender, pack years, and airflow obstruction

With the exception of %LAA-950, all morphologies were measured by the LH method at the level of the secondary pulmonary lobule.

But even if we can better diagnose cancer among the many screen detected nodules, not all patients with lung cancer die of it…

Table 7. Cause of Death on the Death Certificate, According to

Cause of Death	Low-Dose CT Group
Neoplasm of bronchus and lung†	427/1865 (22.9)
Other neoplasm	416/1865 (22.3)
Cardiovascular illness	486/1865 (26.1)
Respiratory illness	175/1865 (9.4)
Complications of medical or surgical care	12/1865 (0.6)
Other	349/1865 (18.7)

17% of patients diagnosed with screen detected lung cancer died of something else*…

Can we use CT features to predict who is likely to die of lung cancer?

** Screen detected in years T0-T2; NLST-163 PI: Kinsey*

Are Tumors that Occur in Regions of Emphysema Associated with a Worse Prognosis?

Regional tumor emphysema

Approach:

-263 cases from the MGH-LCS study

-Classified tumors by region

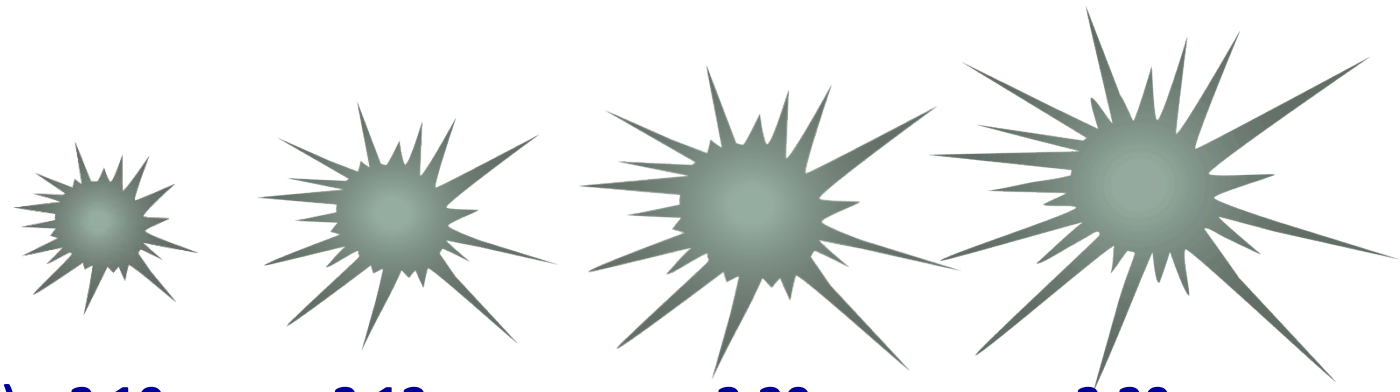
-Compared with regional LAA-950% score

-Survival analysis

MGH-LCS: Massachusetts General Hospital Lung Cancer Susceptibility Study, PI: DC Christiani

Tumors occurring in regions of emphysema are larger

Tumor Emphysema Quartile (⇧): 1st 2nd 3rd 4th



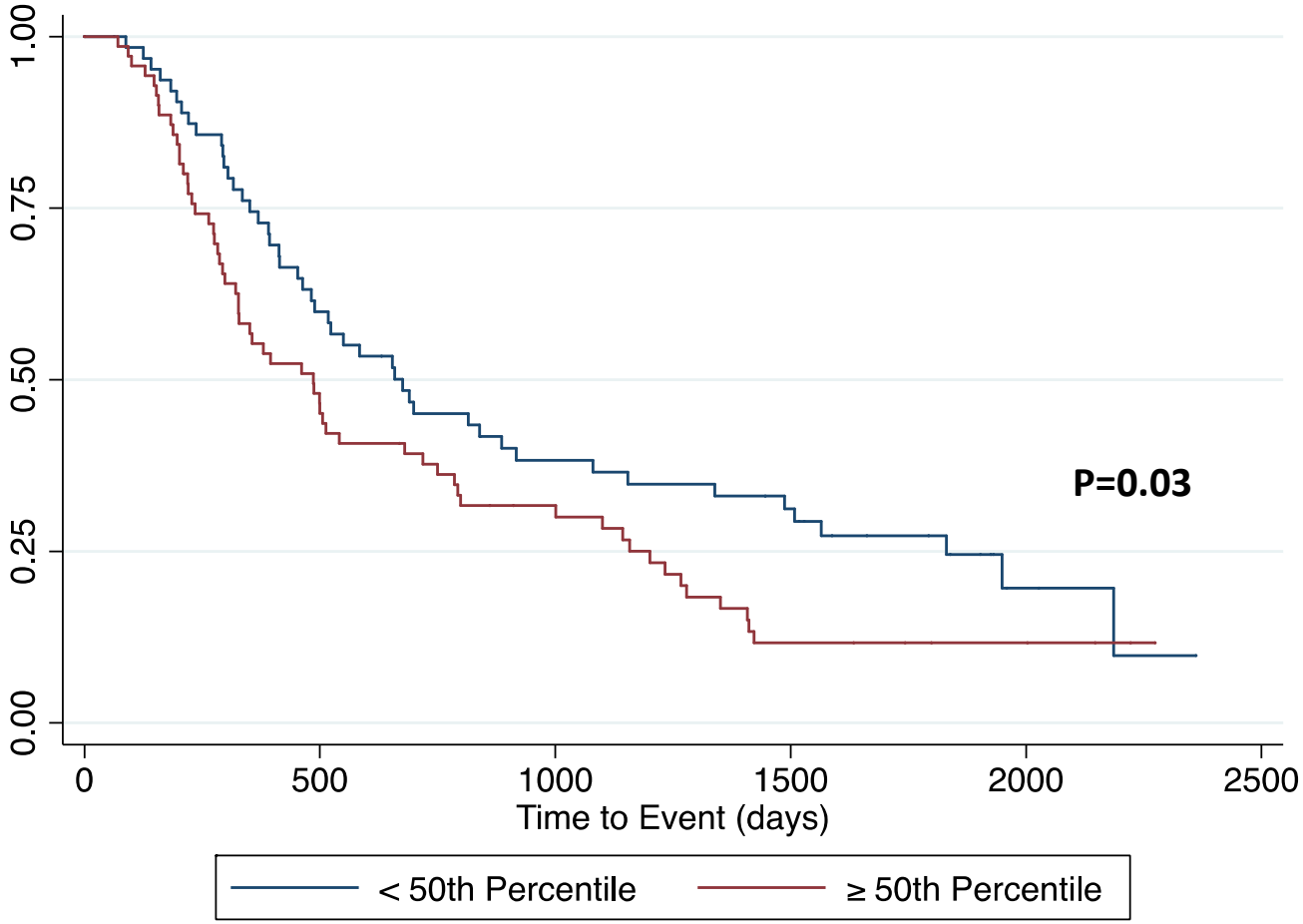
Diameter (cm): 3.10 3.12 3.20 3.30

Linear Trend for Tumor Size

	OR	CI	P
Tumor Emphysema	3.51	[0.47, 6.58]	0.025

Kinsey CM, San Jose Estepar R., et al. *Ann Am Thorac Soc*. Aug;12(8):1197-205.(2015)

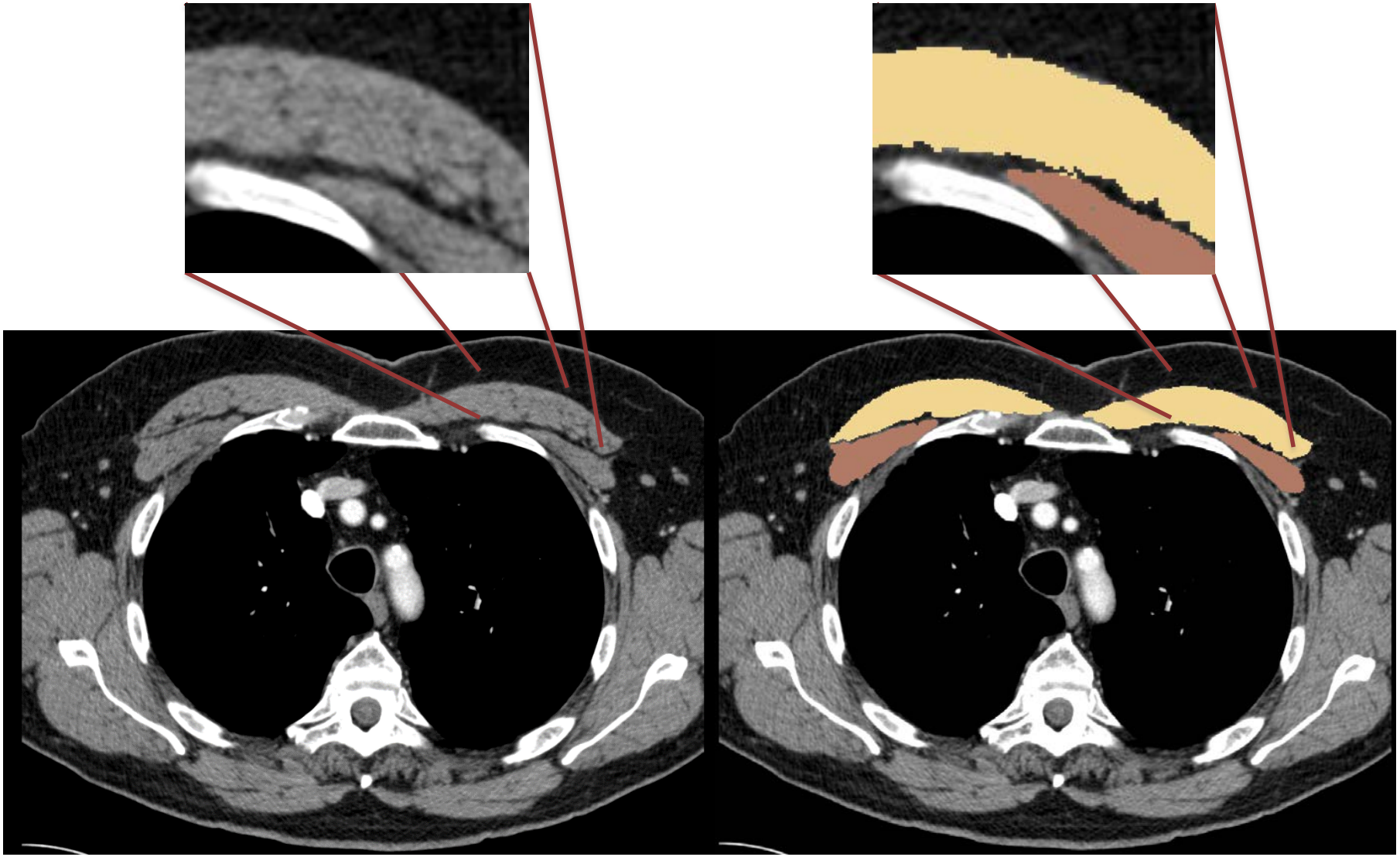
Tumors occurring in regions of emphysema are associated with a worse overall survival



OR_{adj} 1.03 [1.01, 1.05], P=0.0006, adjusted for age, sex, histology, stage, central tumor location, performance score, and surgery

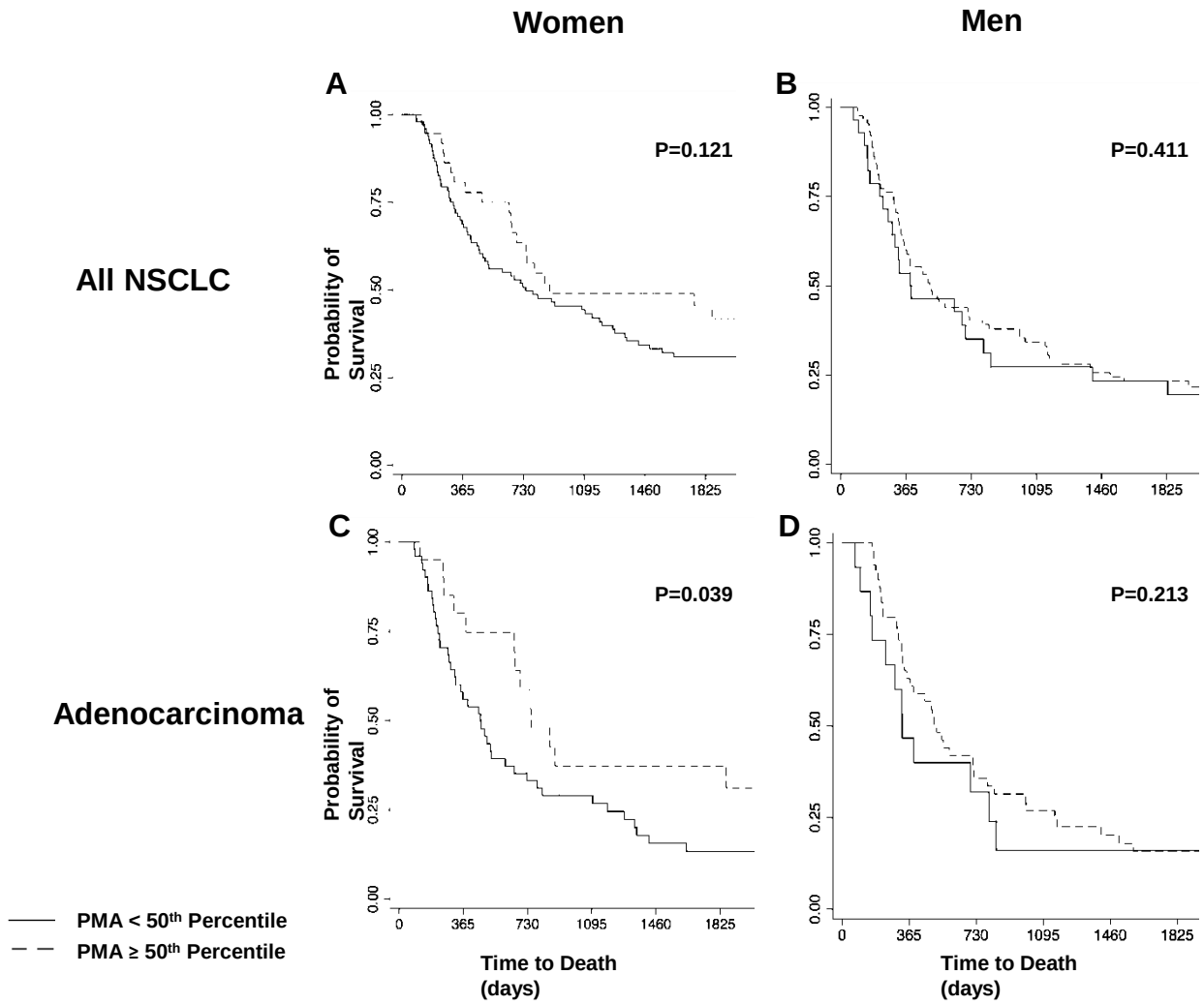
Kinsey CM, San José Estépar R., et al. *Ann Am Thorac Soc*. Aug;12(8):1197-205.(2015)

Non-parenchymal features features of COPD and LC death



N=263

Lower pectoralis muscle area is associated with a worse prognosis for NSCLC



OR_{adj} 0.97 [0.96, 0.99], P=0.002, adjusted for age, sex, smoking, histology, stage, performance score, and surgery

Kinsey CM, San José Estépar R., et al. *Canc Epidemiol Biomarkers Prev*. 2016 May 19. [Epub ahead of print]

Limitations of the presented data:

1) None of these data are “predictive”

2) Many of these data are not derived from a CT screening population

3) All survival data and analyses are subject to secular trends in lung cancer care (e.g approach to ground glass nodules, immunotherapy, etc)

Predominantly serve as examples and discussion points…

Demonstrates the need for a prospective system of evaluation which includes the ability to test interventions and continuously monitor lung cancer mortality.

Balancing Risks: Unanswered Questions and Opportunities

1) **29% of LC deaths in the NLST were not screen detected. How careful do we need to be with changes to CT screening? Changes in sensitivity need to be considered as drivers of mortality.**

2) **96% of positives in the NLST were not cancer. Can we improve detection of cancer among the many indeterminate nodules? Emphysema morphology is associated with lung cancer and may make it valuable as part of a prediction model.**

3) **17% with CT screen detected lung cancer in the NLST died of something else. Can we predict who will die of lung cancer? This is the actual endpoint of CT screening. Features such as regional emphysema and body composition (pectoralis muscle area) may be helpful.**

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