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Disclosures

- I have no conflicts of interest.
- I am discussing lung cancer screening with low-dose helical CT and CXR. Neither has been approved for screening by the FDA.

Results from the National Lung Screening Trial

- Trial Design and Initial Trial Results
- False-positive Rates and Evaluation of a Positive Screen
- Quality Assurance | Radiation Dose with Low-Dose Chest CT in the NLST
- Important Forthcoming NLST Studies of the Impact of Screening

NLST design

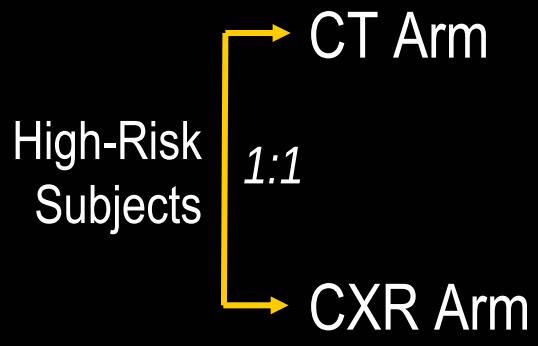
Prospective, randomized trial comparing low-dose helical CT screening to chest x-ray screening with the endpoint of lung cancer specific mortality in high risk participants

Eligibility

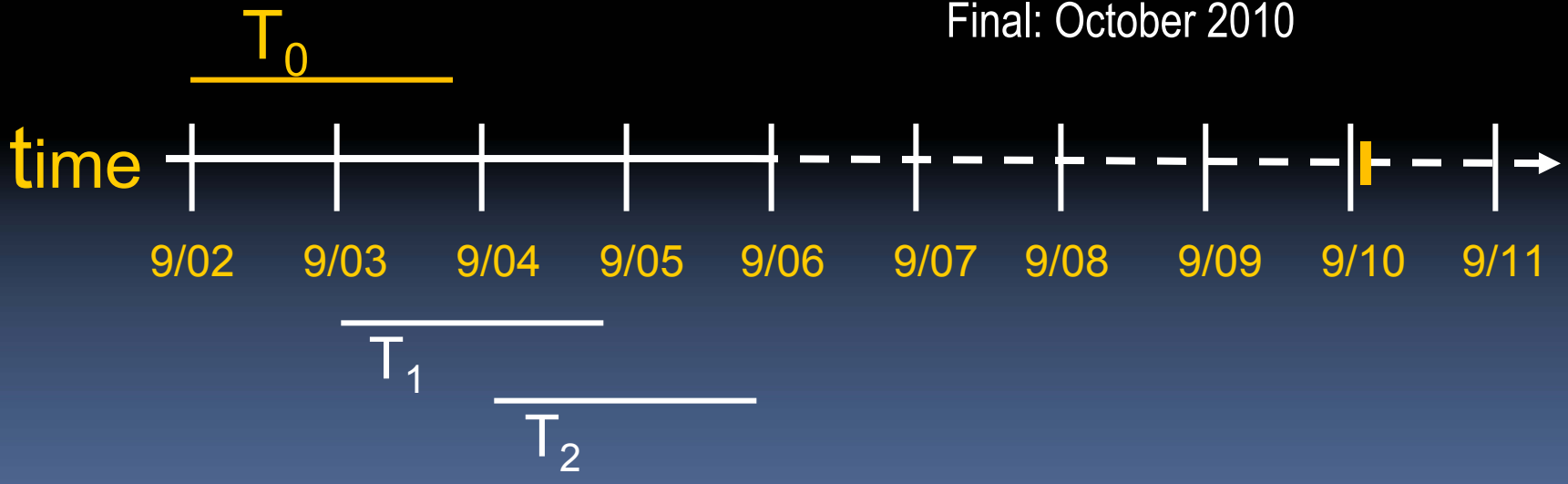
- Age 55-74
- Asymptomatic current or former smoker; 30 pack year smoking history
- Former smokers: quit within preceding 15 years
- No prior lung cancer diagnosis
- No evidence of other cancer within preceding 5 years

http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full

NLST design and projected timeline

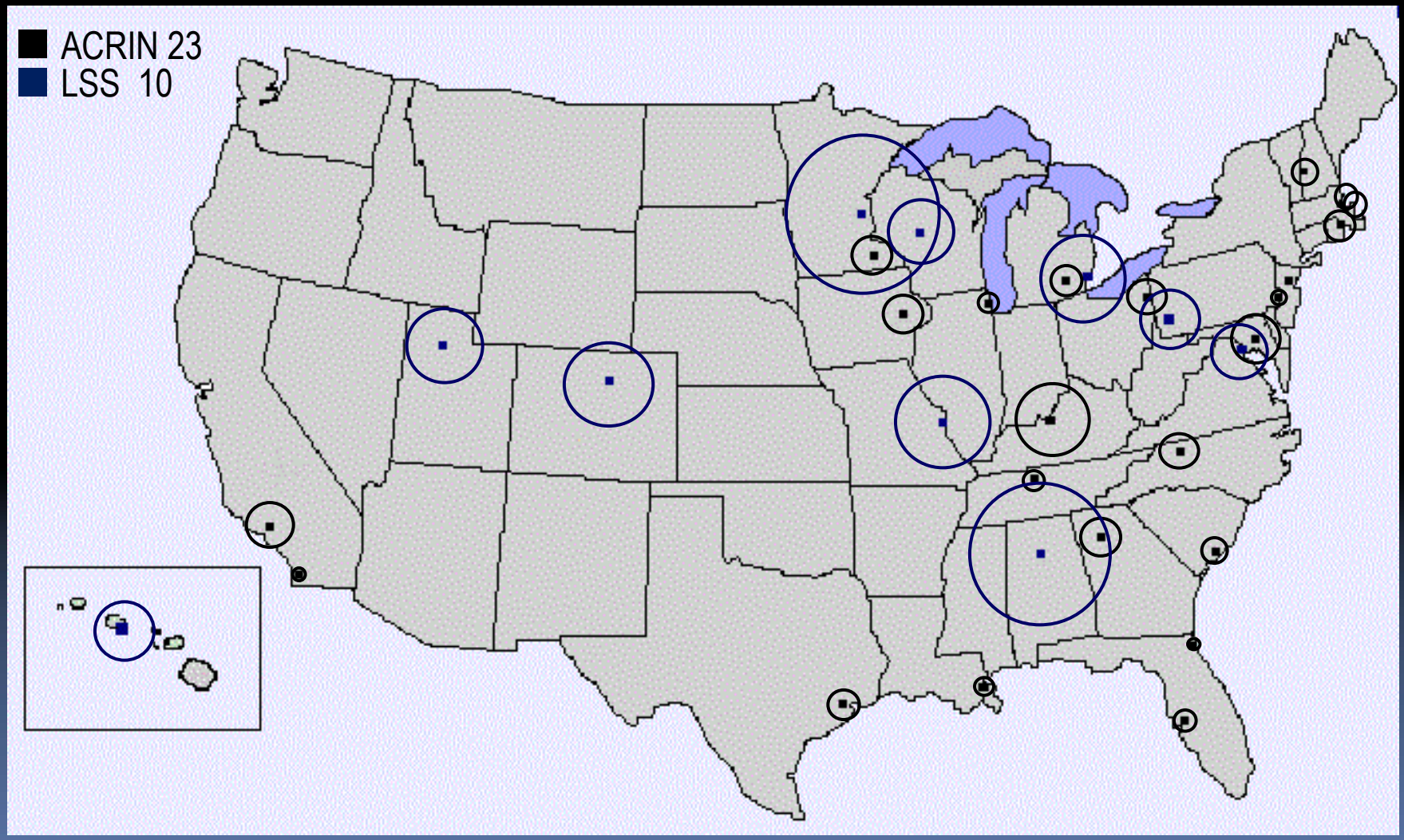


Annual Interim Analyses : 4/2005 - 4/2010
Final: October 2010



http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full

Participating sites



NLST primary endpoint

	Helical CT vs. CXR
Lung cancer-specific mortality	20% difference
α	5%
Power	90%
Compliance	85% CT | 80% CXR
Contamination	5% CT | 10% CXR
Size	25,000 / arm

http://radiology.rsna.org/content/early/2010/10/28/radiol.10091808.full

NLST secondary endpoints

- Secondary endpoints
  - All cause mortality
  - Lung cancer: prevalence | incidence | interval cancers
  - Stage distribution
  - Screening test performance
  - Medical resource utilization for [+] screen

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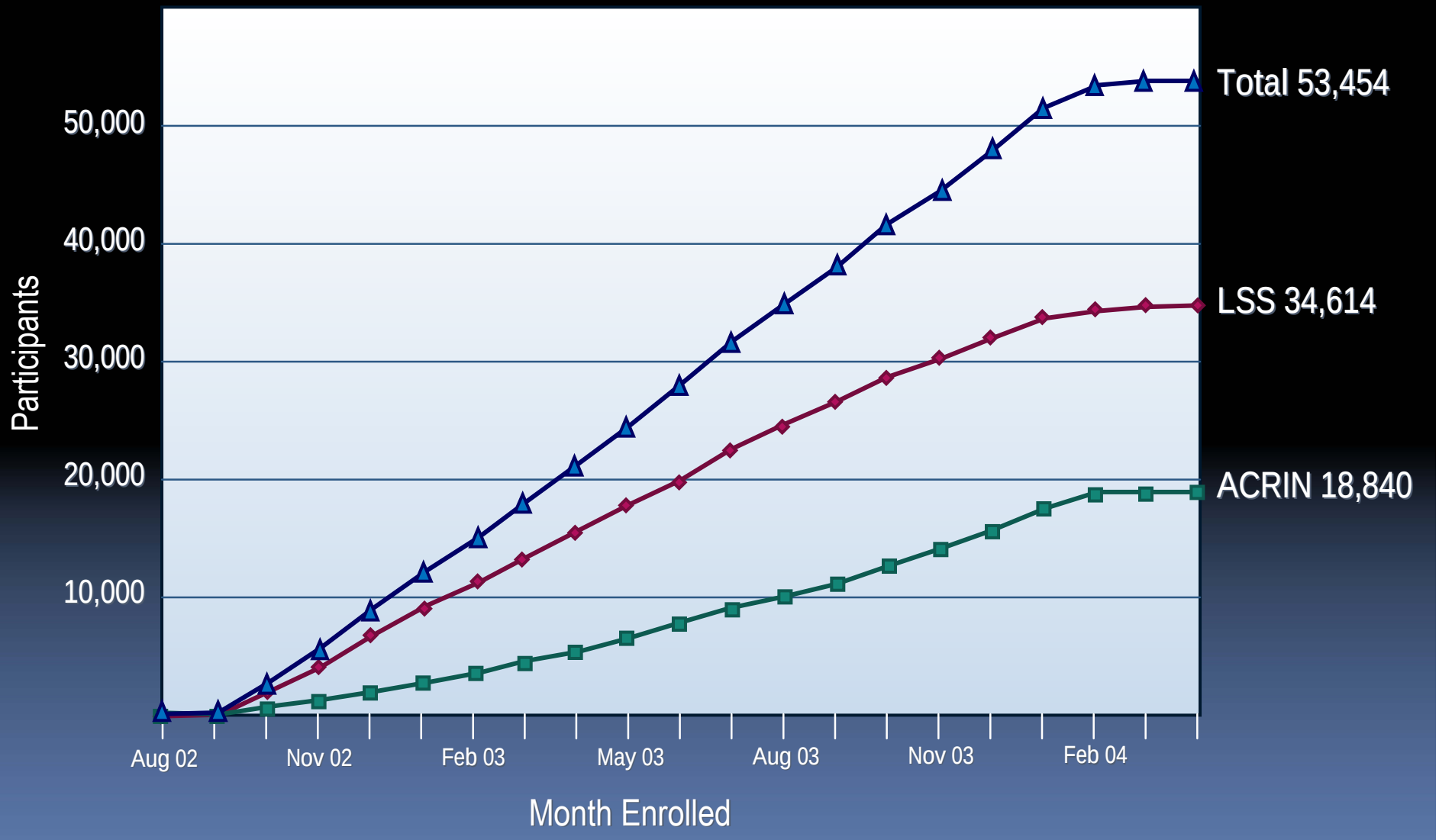
NLST cumulative accrual – 33 sites



Comparison to US census data

- United States Census Dept Tobacco Use Supplement of Continuing Population Survey for 2002-2004
- Contains information on 240,000 respondents
- Subset of respondents aged 55-74, with 30+ pack year smoking, either current smoker or former smoker who quit within the past 15 years
- Identified smoking status, age, sex, race, ethnicity, marital status, and education

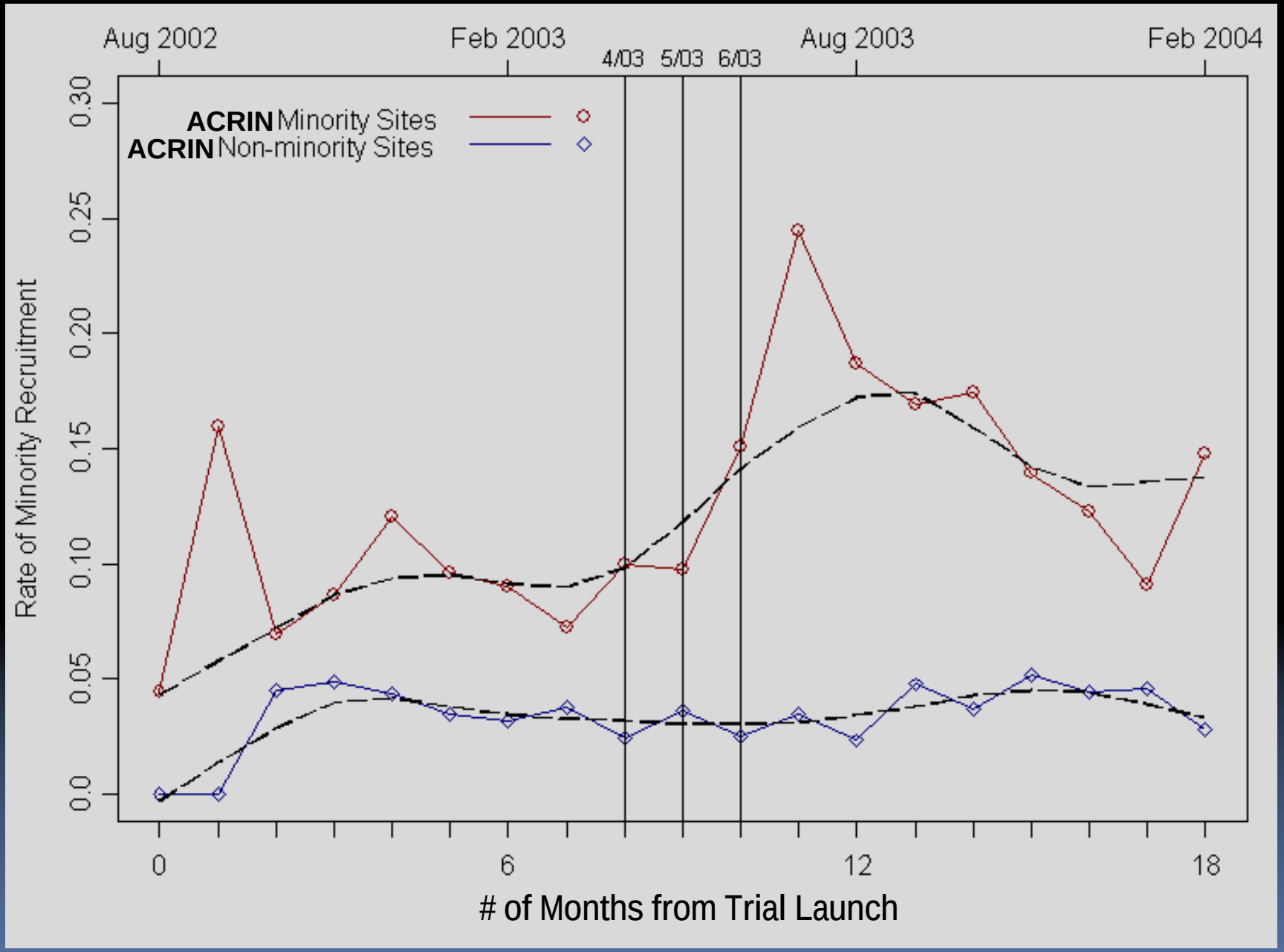
Comparing NLST with eligible US census population

53,454 participants	NLST	US Census
Male (%)	59.0	58.5
Age		
55-59 (%)	42.8	35.2
60-64 (%)	30.6	29.3
65-69 (%)	17.8	20.8
70-74 (%)	8.8	14.7
Race | Ethnicity		
Black (%)	4.4	5.5
Hispanic (%)	1.7	2.4
Current smoker	48.2	57.1
Median pack yrs	48.0	47.0

JNCI J Natl Cancer Inst (2010) 102 (23): 1771-1779.

NLST minority recruitment efforts

Institution	Location	Population of Interest
Emory University	Atlanta, GA	African American
Jewish Heart and Lung	Louisville, KY	African American
Johns Hopkins University	Baltimore, MD	African American
M.D. Anderson Cancer Center	Houston, TX	Hispanic
St. Elizabeth's Health System	Youngstown, OH	African American
UCLA Jonsson Cancer Center	Los Angeles, CA	African American, Hispanic, Asian
Wake Forest University	Winston-Salem, NC	African American
University of Alabama Birmingham	Birmingham, AL	African American
University of Colorado	Denver, CO	Hispanic
Henry Ford Hospital	Detroit, MI	African American
Pacific Health Research and Education Institute	Honolulu, HI	Asian, Pacific-Islanders


Aug 2002
Feb 2003
4/03
5/03
6/03
Aug 2003
Feb 2004
ACRIN Minority Sites
ACRIN Non-minority Sites
Rate of Minority Recruitment
0.0
0.05
0.10
0.15
0.20
0.25
0.30
0
6
12
18
# of Months from Trial Launch

Screening exam compliance

Study Year	Helical CT		Chest X-ray		Total	
	Expected	Screened	Expected	Screened	Expected	Screened
T0	26,713	98.5%	26,722	97.5%	53,435	98.0%
T1	26,282	94.0%	26,398	91.3%	52,680	92.6%
T2	25,935	92.9%	26,097	89.5%	52,032	91.2%

Screen positivity rate by screening round & arm

	Low dose helical CT			CXR		
	Number screened	Number positive	% Positive	Number screened	Number positive	% Positive
Screen 1	26,314	7,193	27.3	26,049	2,387	9.2
Screen 2	24,718	6,902	27.9	24,097	1,482	6.2
Screen 3	24,104	4,054	16.8**	23,353	1,175	5.0**
All screens	75,136	18,149	24.2	73,499	5,044	6.9

* Positive screen: nodule ≥ 4 mm *or* other findings potentially related to lung cancer.

** Abnormality stable for 3 rounds *could* be called negative by protocol.

True and false positive screens

Screening Result	Low Dose Helical CT			CXR		
	Screen 1 N (%)	Round 2 N (%)	Round 3 N (%)	Round 1 N (%)	Round 2 N (%)	Round 3 N (%)
Total Positives	7,193 (100)	6,902 (100)	4,054 (100)	2,387 (100)	1,482 (100)	1,175 (100)
Lung cancer	270 (4)	168 (2)	211 (5)	136 (6)	65 (4)	78 (7)
No lung cancer	6,923 (96)	6,734 (98)	3,843 (95)	2,251 (94)	1,417 (96)	1,097 (93)

Data reflect the final interpretation, including benefit of historical comparison exams.

Endpoint verification

- All death certificates obtained
- Independent endpoint verification committee
- Selection algorithm includes
  - All lung cancer deaths | treatment-related deaths
  - Indeterminate cancers or deaths
  - Deaths within specific time intervals post screening exams | COPD
  - Deaths within 6 months of [-] screens with significant *other* findings
- Chart review of cause of death
  - Review blinded to screening arm and death certificate

Interim analysis: lung cancer mortality 10-20-2010

Arm	Person Years (py)	Lung cancer deaths	Lung cancer mortality per 100,000 py	Reduction in lung cancer mortality (%)	Value of test statistic	Efficacy boundary
CT	144,097.6	354	245	20.3	–3.21	–2.02
CXR	143,363.5	442	308			

p = 0.0041

Deficit of lung cancer deaths in CT arm exceeds that expected by chance, even allowing for multiple looks at the data.

CXR arm compared with matched 30,000 cohort in PLCO, no benefit of CXR seen.

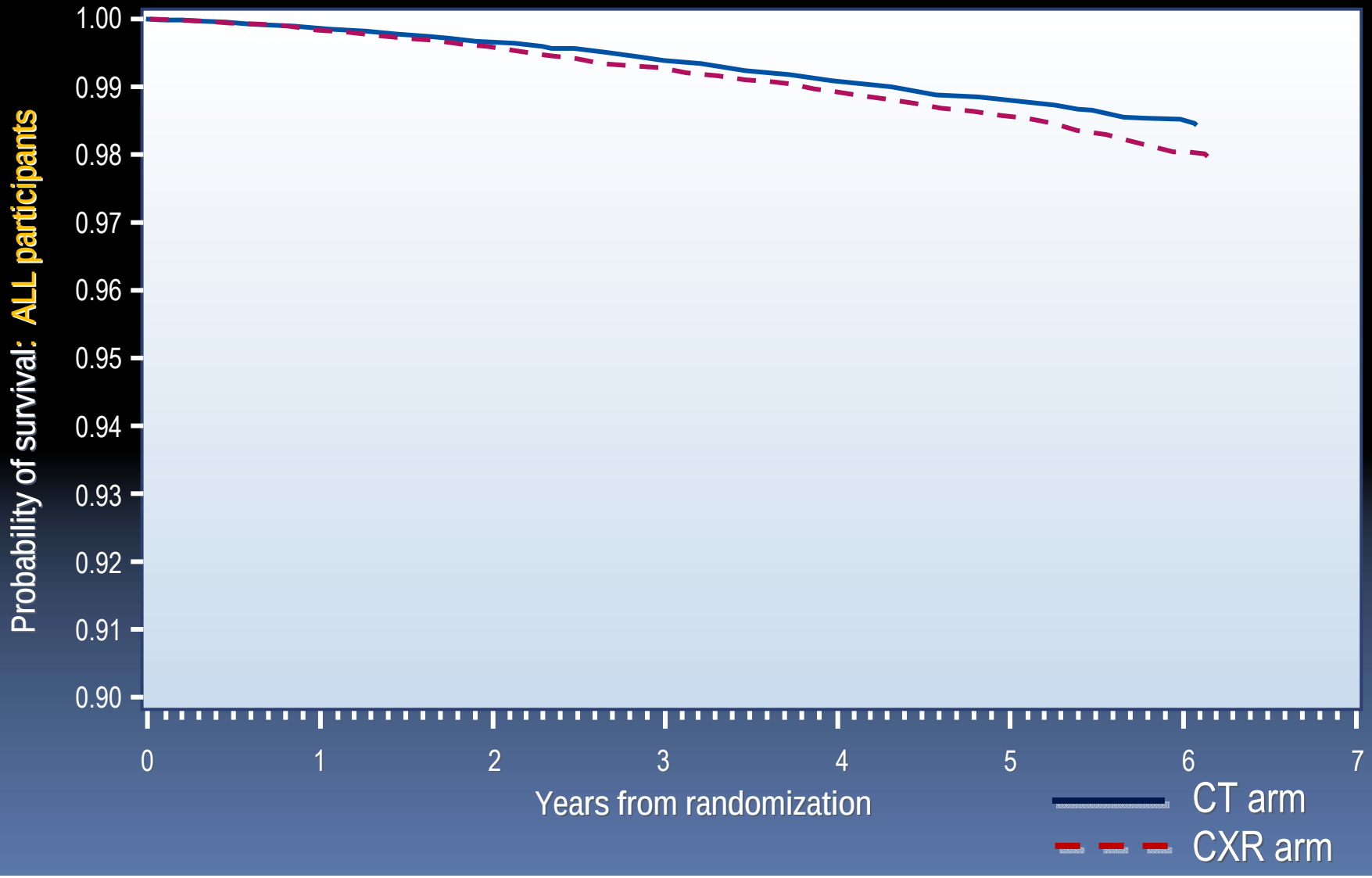
Interim analysis: all-cause mortality 10-20-2010

Arm	Person Years (py)	Deaths	All-cause mortality per 100,000 py	Reduction in all cause mortality (%)	Value of test statistic	Value for significance
CT	167,389.9	1870	1117	6.9	–2.27	–1.96
CXR	166,328.2	1996	1200			

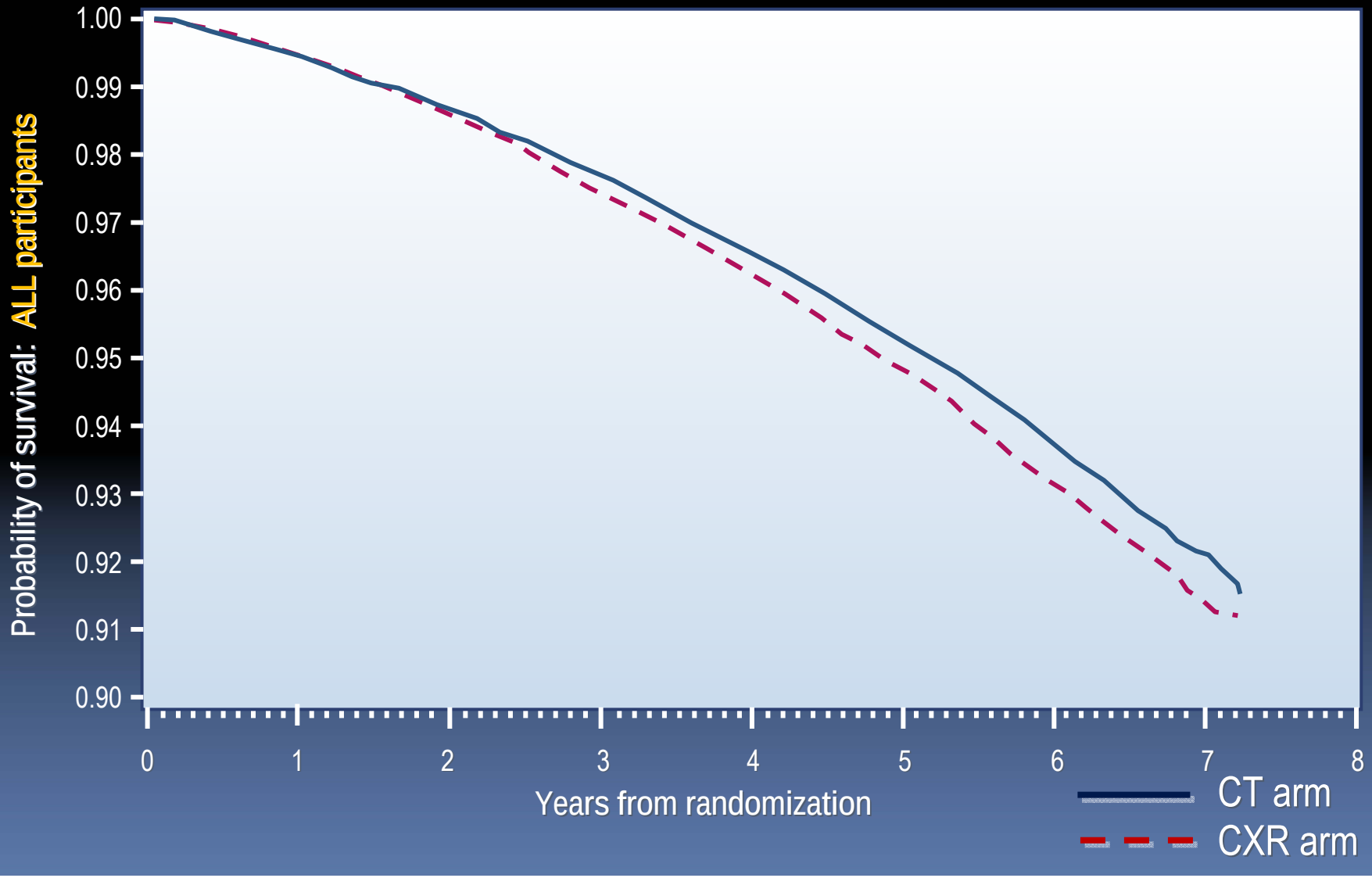
p = 0.023

- Lung cancer: 25% of all deaths in NLST
- Lung cancer: 56% of 126 excess deaths in CXR arm

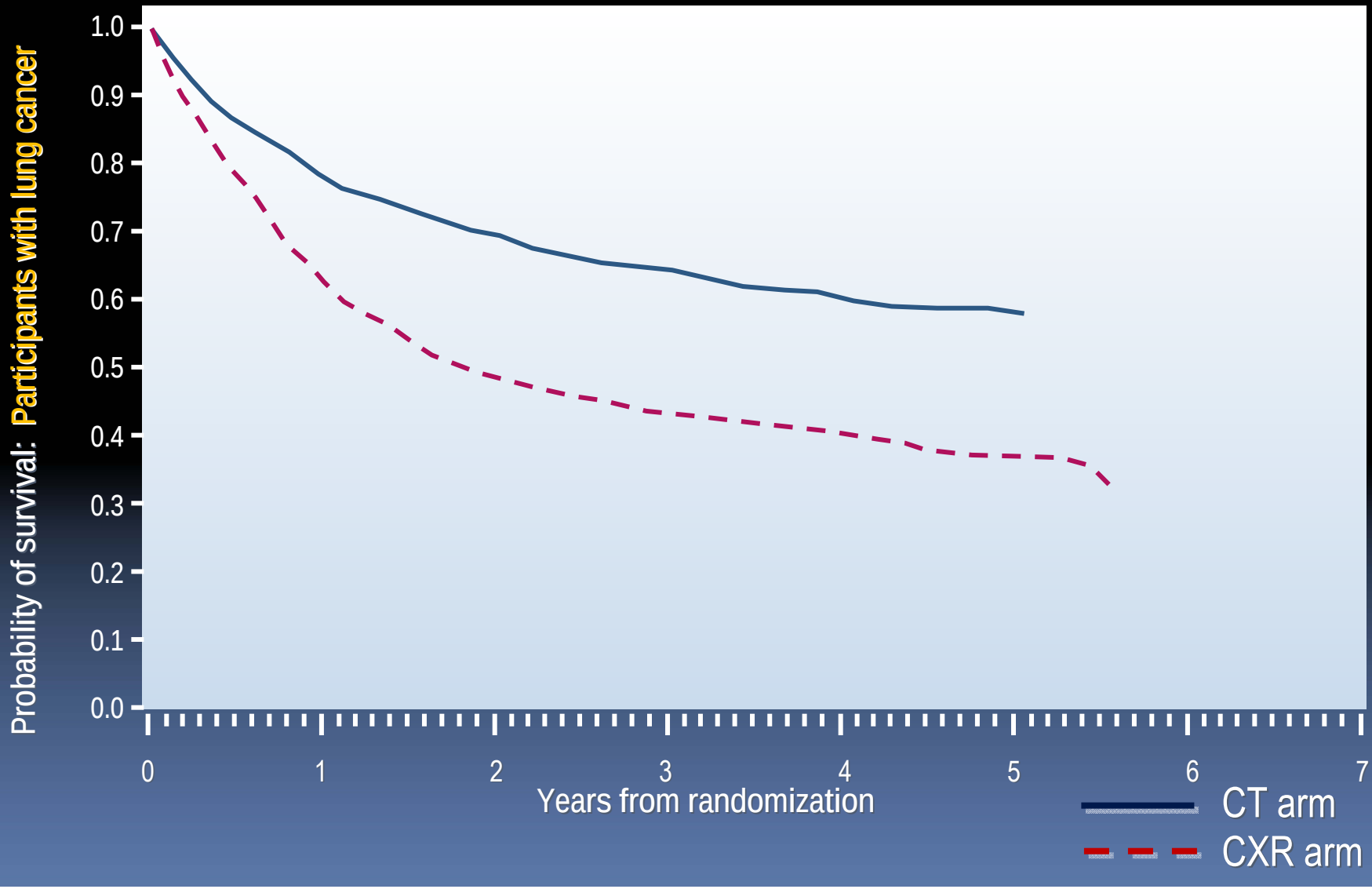
Kaplan-Meier curves for *lung cancer mortality*



Kaplan-Meier curves for *all-cause mortality*



Lung cancer case survival Kaplan Meier curve



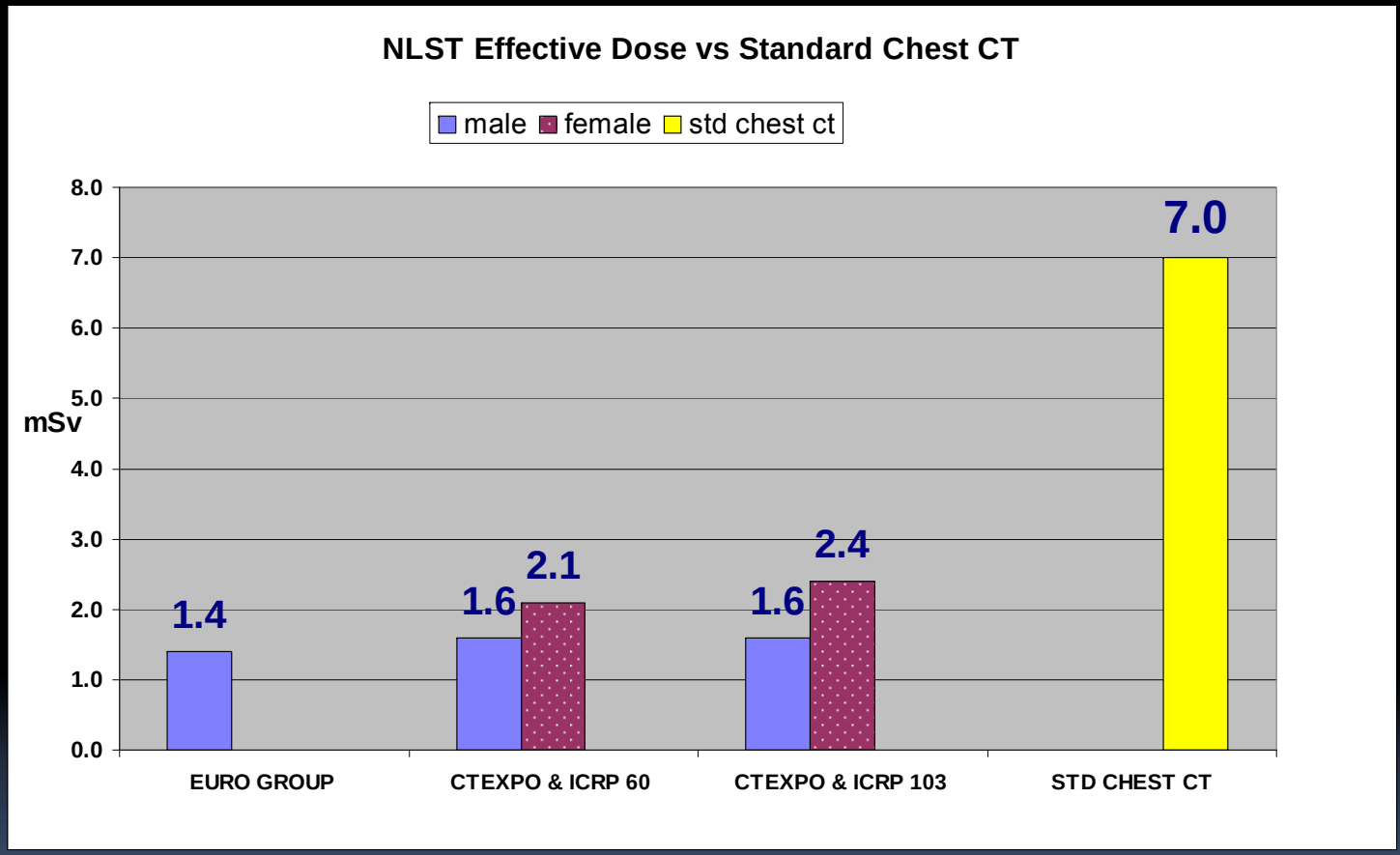
NLST CT Technique Chart Parameter
kV
Gantry rotation time
mA (Regular patient | Large patient values)
mAs (Regular | Large)
Scanner effective mAs (Reg | Large)
Detector collimation (mm) – T
Number of active channels – N
Detector configuration- N x T
Collimation (on operator console)
Table incrementation (mm/rotation) – I
Pitch ([mm/rotation]/beam collimation) – I/NT
Table speed (mm/second)
Scan time (40 cm thorax)
Nominal reconstructed slice width
Reconstruction interval
Reconstruction algorithm
Images/dataset (40 cm thorax)
CTDI vol (Dose in mGy)

NLST imaging standardization

- CT Technique Chart
  - Standardized 18 parameters
  - 14 CT scanners: 4-64 channels
  - 120 kV; mAs < 80 (CTDIvol 2-3mGy)
  - Nominal slice thickness: ≤ 2.5 mm
- Equipment certification annually
- Routine CT phantom calibration
- CXR techniques from CRFs & machine output
  - mR/mAs vs. kV
- Manual & automated review of DICOM headers
- Subsample had visual QC by radiologists

Cagnon CH. Acad Radiol 2006; 13: 1431-1441.

Comparison to Standard Chest CT



- Acceptable chest CT screening can be accomplished at a small fraction of the dose of a standard chest CT

ACRIN-NLST Sub-Studies

- Serial specimen collection for validation of biomarkers (N=10,260)
  - Plasma | buffy coat; sputum; urine annually x 3 yrs
  - Resected lung cancer specimens
  - Available to the research community through proposals acrin.org
- Quality of Life
  - Differential impact of screening of QoL at T0, T1, T2 (SF-36, EQ-5D)
  - Differential impact of [+] screen on anxiety (SF-36, EQ-5D, STAI)

    Administered at T0, 30 days post [+] screen and Q 6 months)
- Formal CEA (in conjunction with RAND)
- Effects of screening on smoking behaviors | beliefs
  - Short and long term

Acknowledgements

NLST Executive Committee

- Denise R. Aberle, MD
- Christine D. Berg, MD
- William C. Black, MD
- Timothy R. Church, PhD, MS
- Richard M. Fagerstrom, PhD
- Barbara Galen, MSN, CRNP, CNMT
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- Barnett S. Kramer, MD, MPH
- David Lynch, MD
- Irene Mahon, RN, MPH
- Pamela M. Marcus, MS, PhD
- Dorothy Sullivan
- Carl J. Zylak, MD

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DCTD, Cancer Imaging Program, Bethesda, MD
American College of Radiology Imaging Network, Philadelphia, PA

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	Fred Larke, PhD	University of Colorado
	Randell Kruger, PhD	Marshfield Clinic
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	Chris Cagnon, PhD	UCLA
	Philip Judy, PhD	Brigham and Women's Hospital
	Randell Kruger, PhD	Marshfield Clinic
	Mike Flynn, PhD	Henry Ford Hospital

NLST Committees

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  * Deceased

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Early Detection Research Group, DCP

ACRIN | Westat | IMS | *CARE* Communications

Our many, many site investigators and research staff

Colleagues NLST ACRIN Tissue Bank & Biomarker Oversight Committee

NLST ACRIN Research Evaluation Panel

ACRIN Specimen Biorepository at University of Colorado

UCLA Tissue Microarray Laboratory

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With appreciation

53,454 trial participants

without whom these studies would not have been possible