

Did death certificates and a mortality review committee
agree on lung cancer cause of death
in the
National Lung Screening Trial?

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Cause of death in cancer screening RCTs

- Primary outcome in cancer screening RCTs is disease-specific mortality
- Accurate assignment of underlying cause of death (COD) is critical
- Two options for COD assignment
 - Mortality review committee (aka death review)
 - More resource-intensive but thought to be more accurate
 - Death certificates (DC)
 - Less resource-intensive but thought to be less accurate

Death review

- Most cancer screening RCTs have used some form of death review
- Is it worth the effort?
- Doria-Rose *et al* (Clin Trials, 2010)
 - Compared DCs to death review
 - Dichotomous* underlying COD for 4 cancer screening RCTs (lung (2), breast, colorectal)
 - Kappa ≥ 0.85 for all

**Example: lung cancer versus not lung cancer*

National Lung Screening Trial (NLST)

- RCT of lung cancer screening with low dose CT versus chest x-ray
 - Heavy and/or long-term smokers
 - Significant 20% lung cancer mortality reduction
- Death review committee
 - 5 MDs, including an MD-epidemiologist
 - Members blinded to arm assignment
 - Determined whether underlying COD was lung cancer (versus not lung cancer)

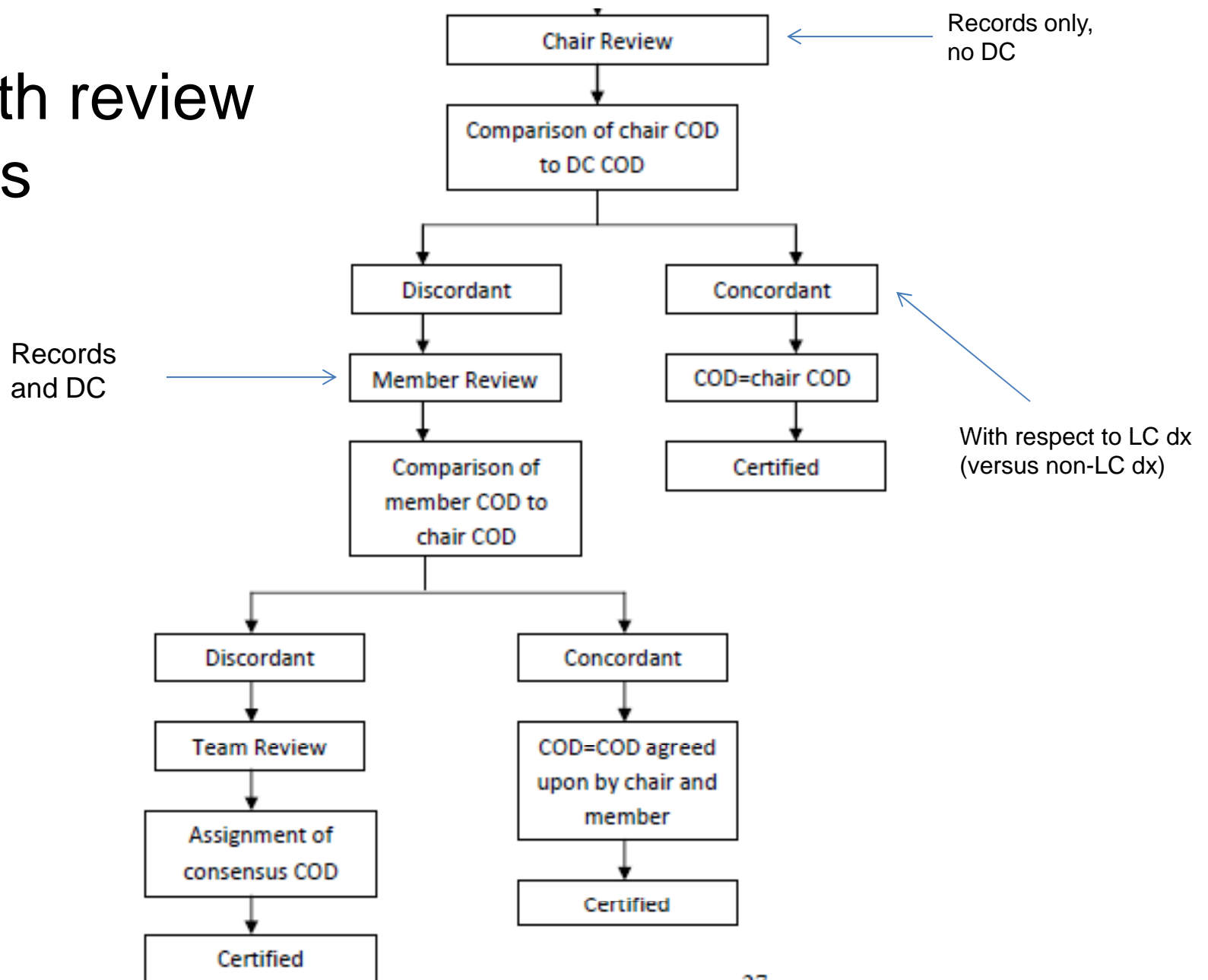
Selection for death review

- Subset of deaths
- Selected by a pre-determined algorithm

Deaths selected for review by algorithm

- Deaths with any DC COD that were most likely to represent a death due to lung cancer (either directly or indirectly)
- Deaths that might have been erroneously assigned a DC lung cancer COD
- Deaths within six months of a screen suspicious for lung cancer
- Deaths within 60 days of certain lung cancer diagnostic evaluation procedures

Death review steps



Analyses

- Gold standard: death review
- Outcome of interest: lung cancer COD
 - Versus COD other than lung cancer
- Performance characteristics of the death certificate COD assignment
- Re-ran final interim analysis
 - Published findings used best available information
 - Would use of DC data only change the conclusion of the study?

Agreement and kappa

Death review

Death
certificate

	Lung cancer	Not lung cancer
Lung cancer	855 (52)	19 (2)
Not lung cancer	84 (5)	685 (42)

Agreement: 94%
Kappa: 87%

1643
(42% of all
deaths)

Performance characteristics

Death review

		Lung cancer	Not lung cancer
Death certificate	Lung cancer	855 (52)	19 (2)
	Not lung cancer	84 (5)	685 (42)
Sensitivity: 91% Specificity: 98%			1643 (42% of all deaths)
PPV: 98% NPV*: 89%			

*DC appears to have missed 9% of lung cancer deaths
(adverse effects of diagnosis or treatment?)

Difference by study arm?

	LDCT (n=825)	Chest x-ray (n=818)
Agreement	0.94	0.93
Kappa	0.89	0.86
Sensitivity	0.92	0.91
Specificity	0.97	0.97
PPV	0.98	0.98
NPV	0.91	0.86

Lung cancer mortality reduction (Final interim analysis)

Best available
information*

20.0%

95% CI: 6.8-26.7

DC only

18.0%

95% CI: 4.2-25.0

**Death review COD for those reviewed; DC COD for others*

Limitations

- About 75% of deaths with a DC COD other than lung cancer (~2079) were not reviewed
 - COD was considered (by the algorithm) unlikely to have been in error with respect to lung cancer death
 - If these deaths had been reviewed and assigned a COD other than lung cancer:
 - Specificity would have been 99%
 - NPV would have been 97%

Limitations

- Generalizability of these findings is limited to lung cancer in persons who meet NLST eligibility criteria

Conclusion

- When assigning lung cancer COD among heavy/long-term smokers, death certificates provide sufficiently accurate information

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Thank you!

DC lung cancer deaths reassigned to other COD by death review

- N=19
- Reassigned to:
 - Other malignancies: 8
 - Respiratory: 6
 - CVD: 3
 - Pneumonia: 1
 - Dementia: 1

DC non-lung-cancer deaths reassigned to lung cancer COD by death review

- N=84
- Reassigned to:
 - Other malignancies: 32
 - CVD: 22
 - Respiratory: 13
 - Other: 13
 - Complications of medical or surgical care: 3
 - Pending at close of study: 1