

# Evaluating the Effectiveness of Surgical Resection of Stage I Lung Cancer

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# Financial and Research Disclosures:

- Dr. David Yankelevitz is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric. As an inventor of these patents, Dr. Yankelevitz is entitled to a share of any compensation which CRF may receive from its commercialization of these patents
- A shareholder in Accumetra LLC
- Medical Advisory Board Carestream Health
- Advisory Panel Pfizer

# **Screening for Lung Cancer With Low-Dose Computed Tomography: An Evidence Review for the U.S. Preventive Services Task Force**

## **Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
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# How effective is surgical resection or SBRT for the Treatment of Early (Stage I) NSCLC?

“The strength of evidence for the effectiveness of surgical resection and SBRT for the treatment of stage I NSCLC is moderate and low for benefit, respectively, downgrading primarily because the evidence came from uncontrolled cohort studies and for imprecision.”

“No RCTs comparing surgical resection or SBRT with no treatment for stage I NSCLC were identified.”

# Why Not Randomize?

Number one cancer killer

When there is an absence of evidence regarding the usefulness of the experimental intervention, this can ethically justify the randomization and is referred to as  **equipoise** . However, this principle also mandates that this approach can only be applied when there is a substantial degree of uncertainty as to whether the treatment would benefit the study participants.

# Why Not Randomize?

Strong evidence from registries that untreated Stage I is highly fatal

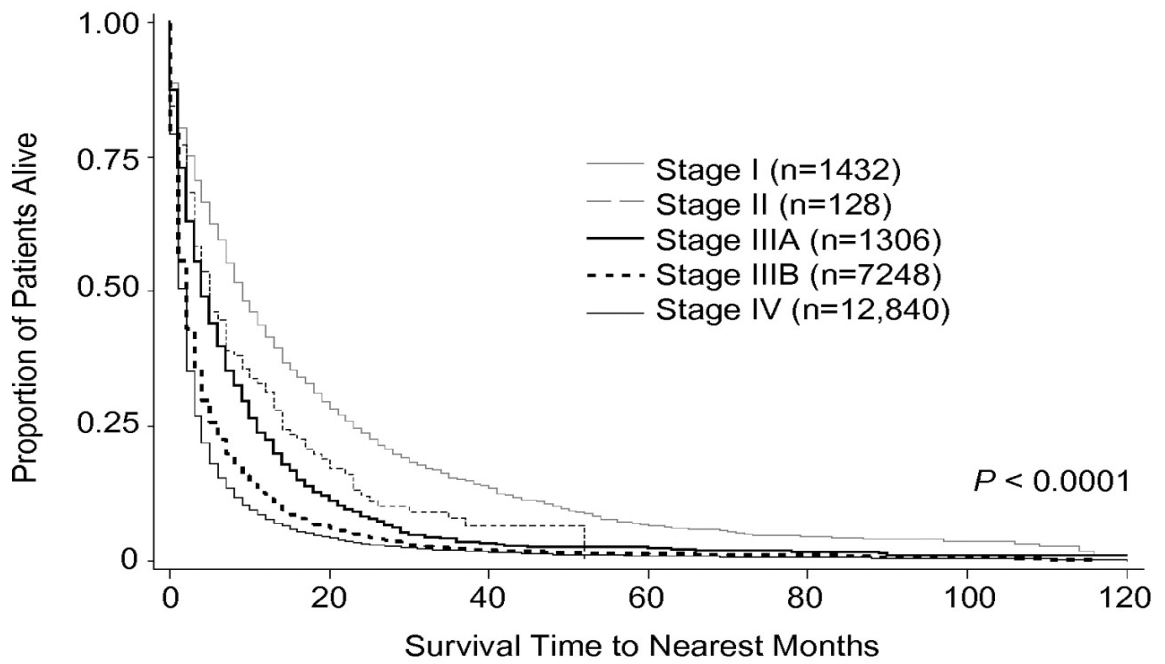
Current staging system is highly dependent on size

Raz DJ et al. Chest 2007

Wao H et al. Syst Rev. 2013

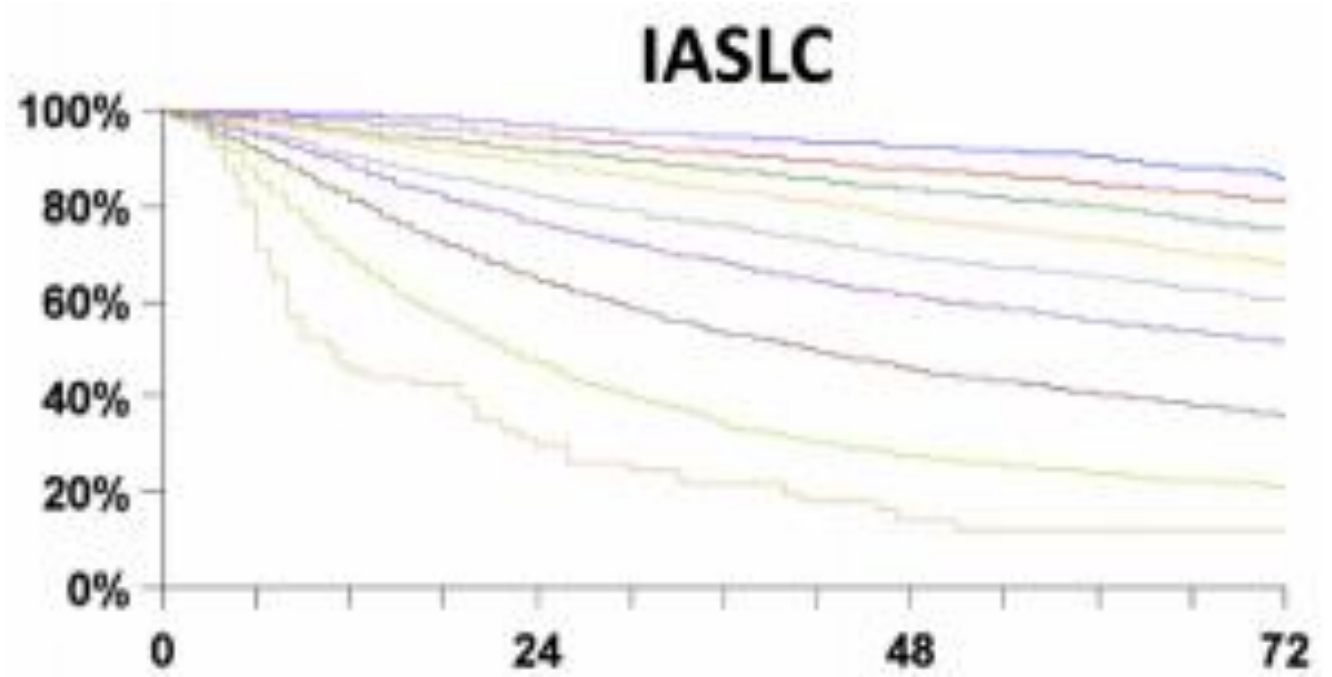
Goldstraw P et al. J Thorac Oncol 2016

NSCLC in California from 1998 to 2003: overall survival for untreated patients with NSCLC, stage I-IV (n = 22,954)



Raz, D. J. et al. Chest 2007;132:193-199

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer



Survival by pathologic stage for eighth edition

Goldstraw P et al. J Thor Onc 2015;11:39-51

# Natural History of Lung Cancer

doubling

1

10

20

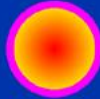
30

40

Single cell  
.001 cm

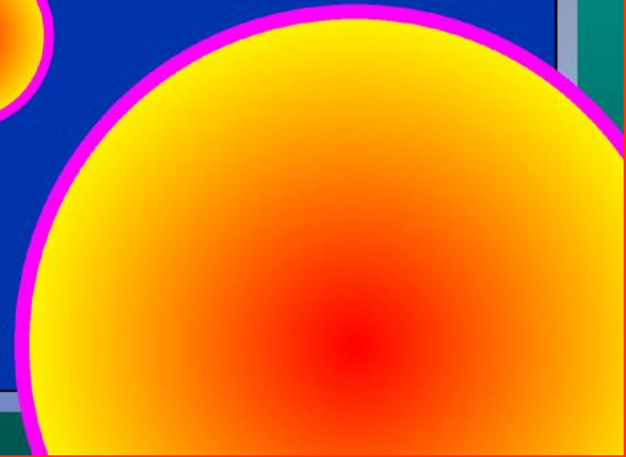
Nodule  
1 cm<sup>3</sup>

Mass  
10 cm<sup>3</sup>



Visability  
on CXR

Death





# Typical Time Course

Consider a 1.0 cm tumor with a doubling time of 60 days (2 months)

Left untreated, at one year (6 D.T's) it would now be 4.0 cm

At two years, death would have already occurred (16 cm)

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## Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

HALLOWAY

Sometime all that is necessary in regard to demonstrating benefit is “common sense”

Strict EBM advocates should volunteer to enroll in a double blind placebo controlled trial

# Rationale for Performing LDCT Screening Trials

- “A major impetus to migrate from chest-x-ray screening to CT screening for lung cancer is the promise of detecting smaller lung cancers. Yet, we do not currently know that outcomes are necessarily better when the cancer is 2 mm as opposed to 20 mm. As purveyors of public policy, we are obliged to avoid the premature endorsement of a screening process before its benefits and liabilities have been reconciled.”

# IDEALLY: Randomized treatment trial

Lung cancers  
diagnosed by  
annual screening

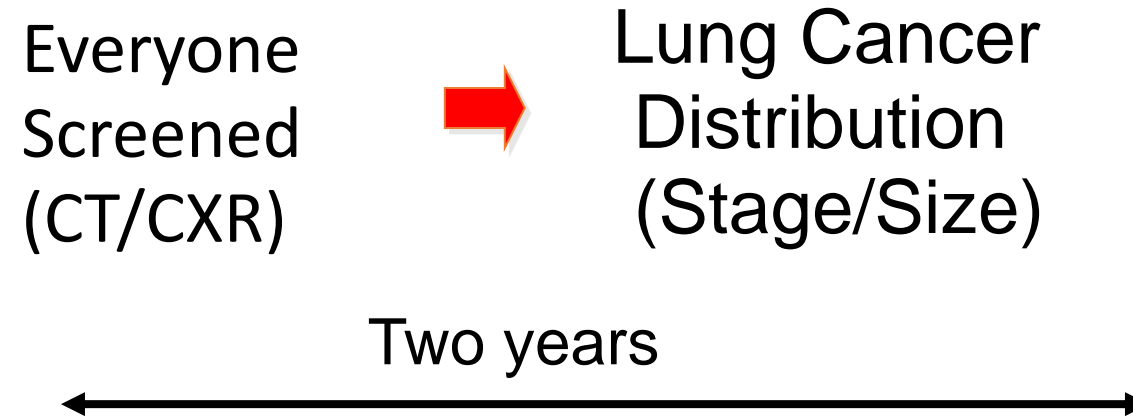
## Prognostic Mission



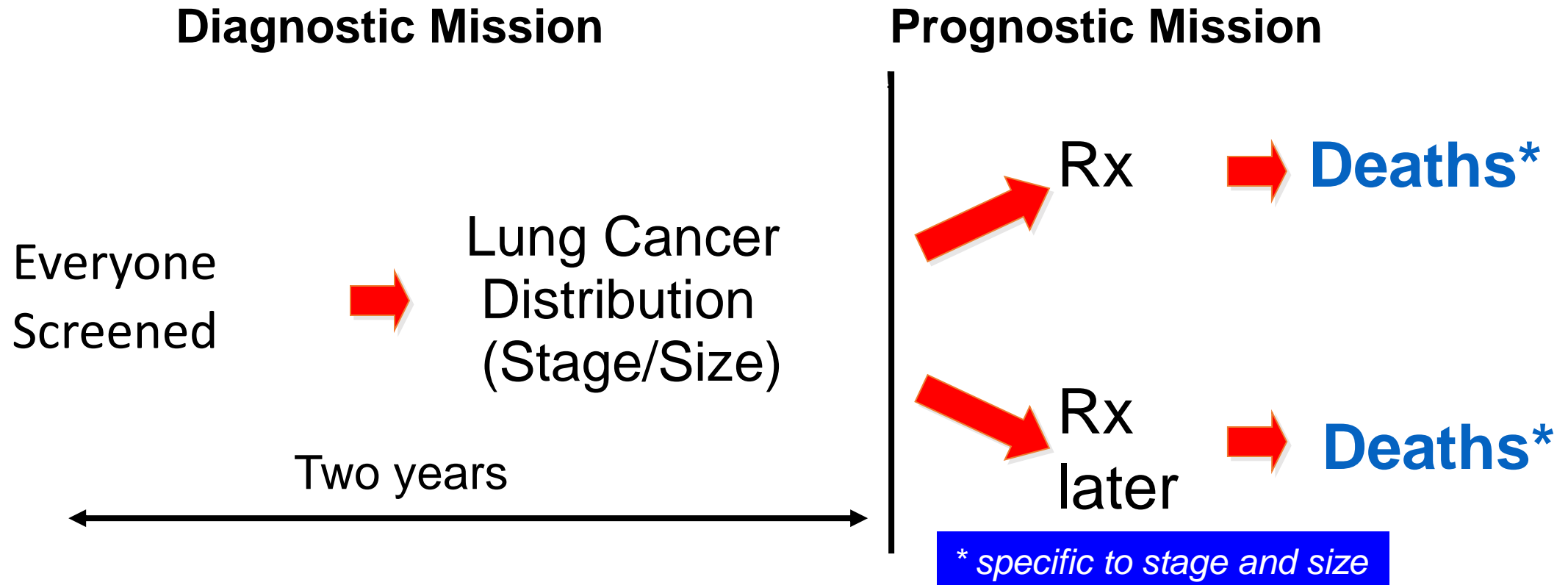
*\* specific to stage and size*

IDEALLY: Direct comparison, both receive same test

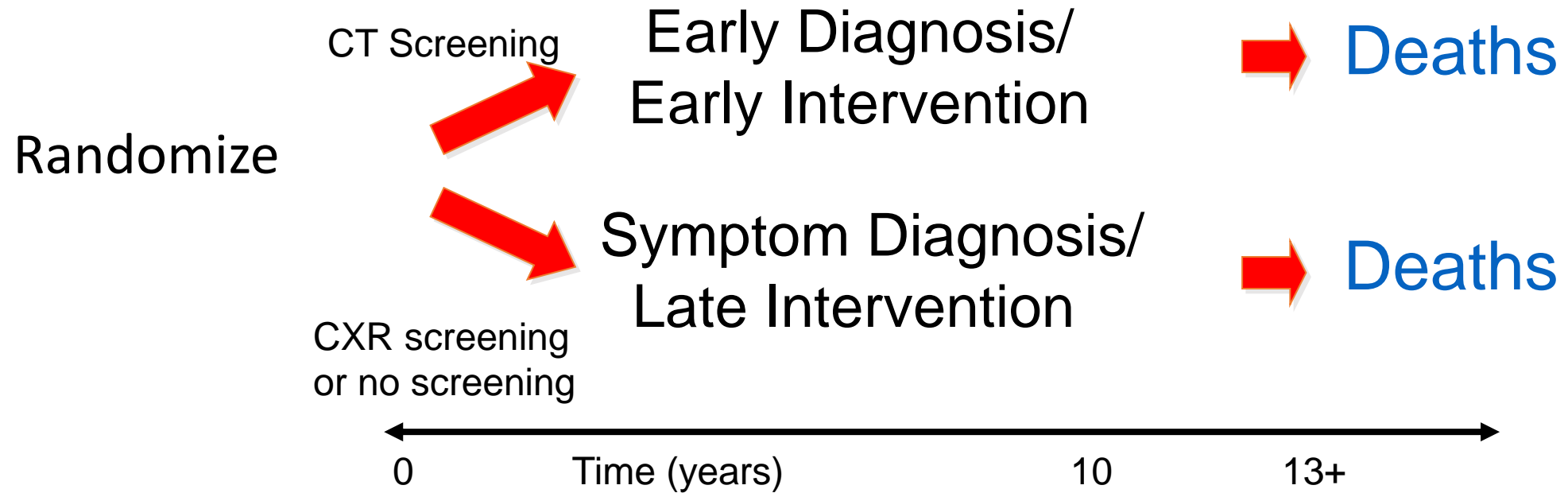
## Diagnostic Mission



Direct approach optimized separately for the diagnostic and therapeutic components.



# Traditional approach (upstream randomization)



# Comparing the Designs

First approach is far more efficient in terms of time of number of participants

Provides information about curability and overdiagnosis and where it occurs

The traditional approach avoids the ethical dilemma of delaying treatment to a person diagnosed with lung cancer (even though we know it is occurring)

Ultimately, both provide the critical endpoint regarding reduction in deaths, in essence randomizing to early and delayed treatment



# Contradictory USPSTF Recommendations

Based on the results of the NLST and NELSON, USPSTF now rates the evidence for the benefit of screening as “high”

At the same time it rates the benefit of the surgical treatment as only “moderate”

The benefit from screening is ultimately from the early treatment that only comes about as a result of early diagnosis

Therefore it should be acknowledged that if the evidence for benefit of screening is high then the evidence for benefit for surgical treatment of Stage I lung cancer must also be “high”

# Conclusion

While the evidence continues to accumulate regarding benefits of screening, its uptake still remains low.

Reports undermining the evidence base for the primary form of treatment only raise additional concerns and cast doubt on the entire screening process

Surgical treatment of Stage I lung cancer is enormously effective, and it should be understood that the evidentiary basis for this should be considered “high”

End