Evaluating the Effectiveness of Surgical Resection of Stage I Lung Cancer

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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.

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

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

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


Natural History of Lung Cancer

- Single cell: 0.001 cm
- Nodule: 1 cm³
- Mass: 10 cm³

Doubling:
- 1
- 10
- 20
- 30
- 40
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)
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

Smith GCS. BMJ 2003
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.”

NLST Protocol
IDEALLY: Randomized treatment trial

Lung cancers diagnosed by annual screening

Prognostic Mission

Rx → Deaths*

Observe until some endpoint → Deaths*

* specific to stage and size
IDEALLY: Direct comparison, both receive same test

Diagnostic Mission

Everyone Screened (CT/CXR)  →  Lung Cancer Distribution (Stage/Size)

Two years
Direct approach optimized separately for the diagnostic and therapeutic components.

Diagnostic Mission

Everyone Screened

Lung Cancer Distribution (Stage/Size)

Two years

Prognostic Mission

Rx

Deaths* later

Rx

Deaths*

* specific to stage and size
Traditional approach (upstream randomization)

Randomize

CT Screening

Early Diagnosis/
Early Intervention

Deaths

Symptom Diagnosis/
Late Intervention

Deaths

0               Time (years)                           10                13+

CXR screening
or no screening
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
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