# Diminished Disease-Free Survival After Lobectomy: Screening Implications

Jerome M. Reich,[1] Jong S. Kim,[2] James W. Asaph[1]

## Abstract

**The reduction in life expectancy imposed by surgical resection of lung tissue is unknown. It was diminished by 7 years (vs. US actuarial figures) in 161 persons with recurrence-free lung cancer after lobectomy. Significance: this harm in overdiagnosed persons will lessen the benefit of lung cancer screening.**

**Background:** The aim of this study was to estimate the effect of lobectomy on life expectancy in healthy smokers and consider the implications for lung cancer screening. **Materials and Methods:** In a retrospective cohort study that provided a minimum of 15 years of follow-up, we analyzed lung cancer survival, all-cause survival, and fatality (1 −survival) of 261 persons with stage I non−small-cell lung cancer who underwent lobectomy at Portland Providence Medical Center between 1978 and 1994. We: (1) compared 5-year disease-free fatality (non−lung-cancer fatality) with lung cancer fatality; and (2) based on actuarial data that demonstrated life expectancy equivalence of the healthiest smokers (whom we assumed would be comparable with subjects judged eligible for lobectomy) in the US population, we compared their long-term, disease-free survival (our primary end point) with actuarial expectations by computing the Kaplan−Meier survival function of the differences between lifetimes since surgery in disease-free persons versus matched, expected remaining lifetimes in the US population. **Results:** (1) Five-year disease-free fatality (16.1%) was 58% as high as 5-year lung cancer fatality (27.6%); (2) disease-free survival was reduced by 6.9-years (95% confidence interval, 5.5-8.3), 41% of actuarial life expectancy (17 years). The divergence from expected survival took place largely after 6 years of follow-up. **Conclusion:** Lobectomy materially diminishes long-term disease-free survival in the healthiest smokers—persons judged healthy enough to tolerate major surgery and to have sufficient pulmonary reserve to sustain loss of one-fifth of their lung tissue. In screened populations, diminished survival in overdiagnosed persons will offset, to an undetermined extent, the mortality benefit imparted by preemption of advanced lung cancer.

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## Introduction

### *Background*

Diminished disease-free survival ($S_{DF}$) as a consequence of surgical resection was advanced as a possible explanation of the counterintuitive outcomes in the 1970s radiographic (CXR) screening trials[1,2] in which lung cancer mortality (a rate; number of cancer deaths per 1000 age-adjusted person-years) was not reduced and all-cause mortality was slightly greater in the screened cohorts despite more than doubling their 5-year cancer survival (a percent).[3] The effect of lobectomy on $S_{DF}$ has not previously been examined. This critical variable directly affects long-term all-cause mortality. Our objective was to estimate the effect of lobectomy on life expectancy in smokers and consider the implications for lung cancer screening. We hypothesized that pulmonary resection materially diminishes life expectancy (measured as $S_{DF}$) in older smokers. This diminution will reduce longevity in persons in whom advanced lung cancer is preempted by screening and in screen-identified persons with overdiagnosed cancer. The primary end points were: (1) all-cause survival ($S_{AC}$), the sum of $S_{DF}$ and cancer survival; and (2) $S_{DF}$, which is rarely specified in reports of lung cancer outcome.

### *Survival Versus Mortality*

Increased cancer survival might be accompanied by either a reduction or an increase in all-cause mortality (ie, longevity).[4] Conversely, diminished survival (increased fatality) will invariably be accompanied by increased all-cause mortality. Screening introduces biases that improve survival without necessarily improving mortality. For example, screening identifies individuals with lung

[1]Thoracic Oncology Program, Earle A. Chiles Research Institute, Portland, OR
[2]Fariborz Maseeh Department of Mathematics and Statistics, Portland State University, Portland, OR

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Address for correspondence: Jerome M. Reich, MD, FCCP, 7400 SW Barnes Rd A242, Portland, OR 97225-7007
Fax: 503-296-4878; e-mail contact: Reichje@isp.com

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cancers not destined to become clinically manifest due either to their slow growth or to intervening, competing, lethal comorbidities. These "clinically irrelevant" cancers are designated "overdiagnosed".[5] Lung cancer survival in overdiagnosed persons is, by definition, 100%; hence: (1) their contribution to net lung cancer survival ($S_{LC}$) is spurious[5]; (2) they can be harmed but not benefited by surgery; (3) a reduction in their $S_{DF}$ will offset the screening benefit received by others in whom advanced lung cancer is interdicted. Mortality is the definitive metric of screening efficacy because it is unaffected by screening-imparted biases—lead time, length-biased sampling, and overdiagnosis (see the Glossary section of Appendix A)—and because it incorporates the consequences of intervention. Augmenting reports of lung cancer mortality with all-cause mortality complements the former by signaling unforeseen or underestimated adverse effects of intervention.

### *Terminology*

Fatality is the complement of survival (1−survival); in percentage terms, fatality % = (100% − survival %). Non-lung cancer fatality ($F_{NLC}$) = $S_{LC}$ − $S_{AC}$—see Appendix A.

## Materials and Methods

### *Design Rationale*

There are insurmountable methodological obstacles to a case-control design for assessing the contribution of surgically-induced diminution of cardiopulmonary reserve to long-term $S_{DF}$: a retrospective design would require a lung cancer case series spanning 20 years, incorporating data on risk factors for early death—pulmonary function, smoking history, diabetes, hypertension, and cardiac status—and a demographically and risk factor-matched control. No extant case or control series encompasses these requirements. Moreover, matching each case to a control by multiple risk factors in addition to age, sex, ethnicity, and surgical decade is not feasible. A prospective randomized study would require approximately 3 decades. It would entail comparison of cancer-free survival in persons who received surgery versus survival in control subjects who did not receive surgery and who did not die of cancer, and would be ethically unacceptable.

A retrospective cohort design circumvents these obstacles. To isolate the effect of lobectomy, we compared the long-term survival after lobectomy of a cohort of persons fit to undergo surgery with recurrence-free, surgical−pathological stage I non−small-cell lung cancer (SILC) with the life expectancy of matched persons in the US population. We justified the use of the US population as the "unoperated cohort" based on its life expectancy equivalent to pooled, life insurance-designated "healthiest smokers." For example, the US life expectancy for a 65-year-old white man in 2001 was 16.5 years versus 16.8 years for a 65-year-old healthy male smoker (Tables 1 and 2).[6] We assumed that life expectancy in our surgical cohort would be comparable with healthiest smokers (See Tables 1, 2 and selection criteria)

We confined our analysis to SILC because it encompasses most screen-identified cases, has the most favorable prognosis, and requires the least extensive resection. Because lesser operations were typically reserved for persons with advanced lung disease, which would have compromised their expected survival, we confined the

**Table 1** Life Expectancy

| Age | All Races | Male Sex | Female Sex | White | White, Male Sex | White, Female Sex | Black | Black, Male Sex | Black, Female Sex |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 77.2 | 74.4 | 79.8 | 77.7 | 75.0 | 80.2 | 72.2 | 68.6 | 75.5 |
| **1** | 76.7 | 74.0 | 79.3 | 77.1 | 74.5 | 79.6 | 72.2 | 68.6 | 75.4 |
| **5** | 72.8 | 70.1 | 75.4 | 73.2 | 70.6 | 75.7 | 68.3 | 64.8 | 71.5 |
| **10** | 67.9 | 65.2 | 70.4 | 68.3 | 65.6 | 70.8 | 63.4 | 59.8 | 66.6 |
| **15** | 62.9 | 60.2 | 65.5 | 63.3 | 60.7 | 65.8 | 58.5 | 54.9 | 61.7 |
| **20** | 58.1 | 55.5 | 60.6 | 58.5 | 56.0 | 60.9 | 53.7 | 50.3 | 56.8 |
| **25** | 53.4 | 50.9 | 55.7 | 53.8 | 51.3 | 56.1 | 49.1 | 45.8 | 52.0 |
| **30** | 48.6 | 46.2 | 50.9 | 49.0 | 46.6 | 51.2 | 44.5 | 41.4 | 47.2 |
| **35** | 43.9 | 41.5 | 46.0 | 44.2 | 41.9 | 46.3 | 39.9 | 36.9 | 42.5 |
| **40** | 39.2 | 37.0 | 41.3 | 39.5 | 37.3 | 41.6 | 35.5 | 32.5 | 38.0 |
| **45** | 34.7 | 32.5 | 36.6 | 34.9 | 32.8 | 36.9 | 31.2 | 28.4 | 33.6 |
| **50** | 30.3 | 28.2 | 32.1 | 30.5 | 28.4 | 32.3 | 27.1 | 24.4 | 29.3 |
| **55** | 26.0 | 24.0 | 27.7 | 26.1 | 24.2 | 27.8 | 23.3 | 20.8 | 25.3 |
| **60** | 21.9 | 20.1 | 23.4 | 22.0 | 20.2 | 23.5 | 19.7 | 17.5 | 21.5 |
| **65** | 18.1 | 16.4 | 19.4 | 18.2 | 16.5 | 19.5 | 16.4 | 14.4 | 17.9 |
| **70** | 14.6 | 13.1 | 15.7 | 14.6 | 13.2 | 15.7 | 13.5 | 11.7 | 14.7 |
| **75** | 11.5 | 10.2 | 12.4 | 11.5 | 10.2 | 12.3 | 10.8 | 9.3 | 11.7 |
| **80** | 8.8 | 7.7 | 9.4 | 8.7 | 7.7 | 9.3 | 8.6 | 7.3 | 9.2 |
| **85** | 6.5 | 5.7 | 6.9 | 6.4 | 5.6 | 6.7 | 6.7 | 5.7 | 7.0 |
| **90** | 4.8 | 4.2 | 5.0 | 4.6 | 4.1 | 4.8 | 5.1 | 4.5 | 5.3 |
| **95** | 3.6 | 3.2 | 3.7 | 3.4 | 3.0 | 3.4 | 3.9 | 3.6 | 4.0 |
| **100** | 2.7 | 2.5 | 2.8 | 2.4 | 2.3 | 2.5 | 3.0 | 2.9 | 3.0 |

All values are given in years. Data from Vital Statistics of the United States, 2001. NVSR Volume 52, Number 14, 2004 (available at: http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_07.pdf); page 3. Information for other years can be found at: http://www.cdc.gov/nchs/products/life_tables.htm.