Mortality benefit from LDCT lung cancer screening

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Abstract

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Introduction: The estimated mortality benefit to current and former smokers of cigarettes from annual lung cancer screening with low dose helical computed tomography (LDCT) is based largely on data obtained from the National Lung Cancer Screening Trial (NLST). As this trial focused on the cumulative benefit at the end of 3 annual rounds of screening, the mortality benefit associated with continued LDCT screening beyond 3 rounds may not yet have been accurately characterized. **Methods and Results:** Time-specific mortality rate ratios were calculated using the NLST data to delineate the yearly mortality benefit. The mortality reduction from LDCT screening was evident by the end of the first year after initial screening and remained consistent at about 20 percent across the years in which there was continued screening. Once screening was stopped, lung cancer mortality among persons in the LDCT screening arm of the trial rose to the levels in the control arm at about 4 years after last screening.

Conclusions: The aggressive nature and short latent period of lung cancer likely account for the

early mortality benefit with just one round of screening. The annual 20% relative mortality reduction in lung cancer from the NLST trial seems to be an accurate representation of the mortality benefit patients may experience from continued yearly LDCT screening even after 3 rounds.

Introduction: Lung cancer is a common cause of death, accounting for 1.7 million lives lost globally in 2015.[1] Public health efforts to rein in lung cancer morbidity and mortality have focused mainly on primary prevention through cessation of cigarette smoking. The advent of low dose helical computed tomography (LDCT), and its usefulness in early detection of lung cancer resulting in reduced lung cancer mortality as demonstrated by the Nation Lung Screening Trial (NLST), have drawn attention to the possibility of secondary prevention of lung cancer through screening of high risk individuals[2]. The U.S. Preventive Services Task Force (USPSTF) recommends annual screening with LDCT in adults aged 55 to 80 years who have at least a 30 pack-year smoking history and currently smoke or have quit within the past 15 years[3]. Prior to screening, individuals are encouraged to have a session of shared decision making and counseling visit with a clinician focused on benefits and harms of screening, follow-up diagnostic testing, over-diagnosis, the possibility of a false positive result, and total radiation exposure.[4] The estimated size of the mortality benefit from LDCT screening is an important factor in the decision-making process.

The NLST was a randomized multicenter study that enrolled 53,454 current and former heavy smokers ages 55- 74 years at 33 U.S medical centers from 2002-2004, and assigned them to undergo three annual screenings with either LDCT or single view chest radiography (CXR). After a median follow up duration of 6.5 years, there were 247 lung cancer deaths per 100,000 person-years in the LDCT group and 309 deaths per 100,000 person-years in the CXR group, resulting in a relative reduction in lung cancer mortality of 20%. An updated analysis after a more complete endpoint verification of lung cancer deaths noted a relative reduction of 16%. [5]

The majority of the available educational material and decision aids for patient and clinician review give the mortality reduction data as obtained from NLST to depict expected benefit from annual screening.[4] However, the mortality impact of cancer screening can vary in the time across a patient's participation in screening. In cancer screening trials, one would expect to see an initial time window right after screening where there would not be a mortality reduction, followed by another period where the mortality reductions become evident and, unless screening is continued, a third window where the mortality rates in the screened group begin to revert to those in the control group. Rather than relying on an average single summary cancer mortality reduction statistic, it is possible to utilize time-specific mortality ratios and mortality rate ratio curves to address the timing and extent of mortality benefit that would be expected from continued screening.[6,7] This analysis explores the utility of using time-specific mortality information to NLST data to estimate the likely mortality reduction that patients may expect with continued annual LDCT screening.[8]

Methods and Results: We accessed the NLST data through the Cancer Data Access system to examine the mortality differences over time. STATA 14 was used for data analysis. The annual mortality rate ratio was calculated by dividing the observed rate of lung cancer deaths among persons in the screening LDCT arm by the corresponding rate among persons in the control arm of the trial. These data reported in Table 1 demonstrate a lung cancer mortality benefit that was manifest during the first year following the initiation of screening, and then was consistently maintained across the additional two years during which screening was provided. Four years after the last screening exam the mortality reduction no longer was evident, though by that time, data were available only on 24% of the participants. The average mortality rate ratio for the first 6 years was 0.82.

Discussion: The reduction in mortality from lung cancer associated with screening by means of LDCT is manifest by the end of one year after initial screening and remains consistent across the years with continued screening. This pattern of results is not necessarily the same for other cancer screening modalities. For example, based on data obtained in the European Randomized Study of Screening for prostate cancer (through measurement of serum levels of prostate specific antigen), the mortality benefit associated with screening is substantially underestimated by the overall difference in cumulative mortality. This results primarily from a delay in the development of a mortality benefit following the initiation of screening.[6] In contrast, the aggressive nature of lung cancer, with 5-year survival of only 18%, and the short latent period of lung cancer would account for the earlier demonstrable mortality benefit by end of one year of follow-up in the NLST.[9] The reduced mortality rate ratio during the several years after completion of 3 rounds of screening in the LDCT likely is due to the early detection and treatment of lung cancers with a longer presymptomatic phase.

As persons in the control arm of NLST received annual screening by means of chest X-rays, the mortality benefit associated with LDCT screening – relative to no screening at all - could have been underestimated. However, there appears to be little if any reduction in lung cancer mortality as a result of chest X-ray screening. [10] On the other hand, the beneficial impact of LDCT screening could increase in the future, with the development of more sensitive and specific scanners as well as the development of more effective treatments for early stage lung cancer.

Conclusion: As the annualized mortality reduction with LDCT screening appeared immediately after initiating screening and continued across each round of screening, the reported overall 20% relative mortality reduction in lung cancer obtained from the NLST trial appears to be an accurate representation of the mortality benefit that would ensue from continued annual screening.

Table 1. Lung Cancer Mortality Rate Ratios in the NLST

Years since randomization		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Lung Cancer Deaths	X-ray		38	70	83	93	87	116	65
	LDCT		31	57	67	84	73	85	72
Mortality Rate Ratio			0.82	0.81	0.81	0.9	0.84	0.73	1.11
Participant Count	X-ray	26,730	26,449	26,090	25,648	25,188	24,675	23,221	6,447
	LDCT	26,722	26,467	26,175	25,814	25,415	24,964	23,473	6,488

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