Benefits and Risks of Lung Cancer Screening

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Lung Cancer Screening: Pro

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Introduction

Lung cancer is the third most common cancer in women and the second most common cancer in men in Germany [1]. It has the highest mortality among the solid tumors. Although there has been progress in the therapy of lung cancer in the last decade, the overall prognosis across all stages has not been substantially improved. Only 15% of patients are alive after 5 years. In contrast, if one looks at other types of cancer such as prostate cancer, colorectal cancer, or breast cancer, substantial improvements in long-term survival have been achieved in the last few years. A large proportion of this positive trend is due to established screening programs for these tumor types. For colorectal cancer, 5-year survival increased from 50% in the 1970s to 62% in the 1990s. For breast cancer, this proportion increased from 75 to 86%. Currently, 97% of patients with prostate cancer are alive after 5 years [2].

There are a number of reasons that make lung cancer screening especially attractive. For one, lung cancers have the highest mortality among the solid tumors worldwide. Also, the prognosis of lung cancer is strictly stage-associated. Treatment is only curative in the early stages. However, only 15–20% of patients are diagnosed in stage I, as the tumors are frequently asymptomatic.

From the 1950s until the 1970s, a number of studies on lung cancer screening were conducted. Usually, these were studies that used chest X-rays for imaging alongside sputum cytology. During this time, a total of four non-randomized non-controlled studies, two non-randomized but controlled trials, and four randomized controlled trials were published on lung cancer screening [3–12]. These studies showed an improved stage dis-

tribution in favor of earlier stages, better resectability of the tumors, and also improved survival. However, an effect on overall mortality could not be demonstrated. Recently, data were published from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [13, 14]. In this large screening trial (n = 154,942), the active-arm participants (n = 77,477), who were aged 55–74 years and had no further specific risk factors, had chest X-rays performed which were compared at baseline and annually repeated for 3 years. Of the 67,038 people screened with chest X-ray, 8.9% had positive findings in their baseline examination, and of these, a diagnosis of lung cancer could be made in 2.1% (n = 126). However, there was no difference in the incidence of lung cancer found between the control group and the screened group. In a mortality analysis, there was no difference in mortality between the screening group and the control group. Thus, the results are comparable to the chest X-ray studies mentioned earlier. When evaluating lung cancer screening studies, a number of methodological problems should be considered. Among these are statistical issues, with a special focus on disease-specific and/or all-cause mortality. Another important factor is the stage shift. As screening yields more frequent diagnoses of early-stage lung cancer, this should result in a reduction in later stages. Last but not least, bias should be considered [15]: i) Lead time bias: screening only leads to earlier diagnosis, but early treatment may not result in increased overall survival; ii) Length time bias: rapidly growing tumors become symptomatic quickly and thus evade the screening, therefore, screening results in the selection of slowly growing tumors; iii) Overdiagnosis bias: an extreme form of length time bias in which very slowly growing tumors are selected that do not affect the prognosis.

Technical advances in imaging techniques for the lung, from chest X-rays to cross-sectional imaging using computed tomography (CT), have led to renewed interest in lung cancer screen-

Table 1. Lung cancer CT screening: results of observational studies (modified from [16])

Author, year	Participants, n	Age, median, years	Non-smokers ^a , %	Pack-years, median, n	CT lesions ^b , n (%)	Baseline ^c , n (%)	Stage I ^d , %	First repeat ^e , n (%)
Henschke et al., 1999	1,000	67	0	45	233 (23)	27 (2.7)	85	–
Sone et al., 2001	5,483	64	54	–	588 (11)	23 (0.4)	100	27 (0.5)
Nawa et al., 2002	7,956	56	38	–	541 (7)	36 (0.5)	78	4 (0.1)
Sobue et al., 2002	1,611	59	14	–	186 (12)	14 (0.9)	71	22 (1.4)
Diederich et al., 2004	817	53	0	45	350 (43)	12 (1.5)	64	–
Swensen et al., 2003	1,520	59	0	45	780 (51)	27 (1.7)	74	13 (0.9)
Pastorino et al., 2003	1,035	58	0	40	199 (19)	11 (1.1)	55	11 (1.1)
Bastarrika et al., 2005	911	55	0	30	291 (32)	12 (1.3)	83	2 (0.2)
Chong et al., 2005	6,406	55	23	–	2,255 (35)	23 (0.4)	56	–
Novello et al., 2005	519	59	0	–	241 (47)	5 (1.0)	67	3 (0.6)
MacRedmond et al., 2006	449	55	0	45	111 (25)	2 (0.4)	50	4 (0.9)
I-ELCAP, 2006	31,567	61	17	30	4,186 (13)	410 (1.3)	85	74 (0.2)
Veronesi et al., 2008	5,201	58	0	44	2,754 (53)	55 (1.1)	66	37 (0.7)
<i>Total</i>	<i>64,475</i>	<i>59</i>	<i>20</i>	<i>–</i>	<i>12,715 (20)</i>	<i>657 (1.0)</i>	<i>81</i>	<i>197 (0.3)</i>

^aNon-smokers, as defined in the respective studies.

^bNumber of participants with suspicious, non-calcifying lesions.

^cNumber of participants with confirmed lung cancer at baseline.

^dPercentage of participants with stage I lung cancer.

^eNumber of participants with confirmed lung cancer at first repeat.

ing. The technique of low-dose CT (LDCT) is based on the fact that even with examination protocols that use less radiation, soft tissue-dense pulmonary nodules of a few millimeters can be detected. Compared to conventional CT from the 1990s, radiation exposure with LDCT is less by a factor of 10. Compared to chest X-ray, radiation exposure with LDCT is 2- to 3-fold higher. In the 1990s, 12 different single-arm non-controlled studies were initiated worldwide (table 1). These feasibility studies were supposed to demonstrate the higher sensitivity of LDCT as compared to conventional chest X-ray [16]. The first two Japanese studies showed a 2- to 3-fold higher rate of lung cancer diagnosis with LDCT as compared to conventional chest X-ray. The American Early Lung Cancer Action Program (ELCAP) enrolled a total of 1,000 participants who were older than 60, had a smoking history of more than 10 pack-years, were functionally operable, and had no cancer history [17, 18]. The screening consisted of an annual CT scan of the thorax and a conventional chest X-ray. This study also showed that LDCT detected 3 times as many non-calcified pulmonary nodules, 4 times as many malignant lesions, and 6 times as many cases of stage I disease. The ELCAP was then extended to the International-ELCAP (I-ELCAP). The I-ELCAP enrolled 31,567 asymptomatic participants for the baseline screening and 27,456 for the follow-up screening. A total of 484 participants were diagnosed with lung cancer. Of these, 412 (85%) had stage I disease, and the 10-year survival calculated for this group was 88% [19]. The other single arm studies were in keeping with these findings. One problem associated with these studies was the high proportion of detected pulmonary nodules and the subsequent surgical treatment of benign nodules. In order to demonstrate the efficacy of lung cancer screening by LDCT, ultimately randomized controlled

studies with the endpoints of disease-specific and overall mortality were required. The single-arm non-randomized non-controlled studies provided the rationale for such an investigation.

Randomized Controlled Studies

On the basis of the feasibility studies, randomized controlled studies were initiated worldwide. The largest trial was the National Lung Screening Trial (NLST). The endpoint was the reduction in lung cancer-specific mortality by at least 20% [20]. Patients enrolled had the following profile: i) age 55–74 years; ii) cigarette smoking history of at least 30 pack-years; iii) former smokers who quit within the past 15 years; iv) asymptomatic and functionally operable; v) no prior malignant disease; and vi) no CT scan within 18 months prior to enrollment in the study. Enrolled patients were randomized to either an LDCT arm with annual screening for 3 years or to a chest X-ray arm also with annual screening for 3 years. Enrollment occurred over 20 months, from August 2002 to April 2004. A total of 53,454 participants were enrolled, and the median follow-up was 6.5 years. Screening with LDCT reduced lung cancer-specific mortality by 20%. A subgroup of the PLCO trial was cross-analyzed with a matched group of the NLST. There was no evidence that screening with chest X-ray alone was significantly different from the control group in the PLCO trial with respect to lung cancer-specific mortality. Furthermore, screening with LDCT was demonstrated to reduce overall mortality by 6.7%. In patients with non-small cell lung cancer, LDCT screening led to a stage shift to earlier stages. This could not be demonstrated for small cell lung cancer. In the screening arm,

Table 2. Results of screening trials: lung cancer-specific and overall mortality (modified from [25])

Study	Male, %	Follow-up, years	Mean age, years	Pack-years, n	Screening intervals, years	Lung cancer mortality, RR (CI)	Overall mortality, RR (CI)
NLST	59	6.5	61	56	0, 1, 2	0.93 (0.86–0.99)	0.80 (0.73–0.93)
DANTE	100	2.8	65	47	0, 1, 2, 3, 4	0.85 (0.56–1.27)	0.83 (0.45–1.54)
DLCST	56	4.8	58	36	0, 1, 2, 3, 4	1.46 (0.99–2.15)	1.37 (0.63–2.97)
MILD	66	4.4	57	39	0, 1, 2, 3, 4	1.80 (1.03–3.13)	1.99 (0.80–4.96)

RR = Relative risk; CI = confidence interval.

129 more patients were diagnosed with lung cancer as compared to the control arm (1,060 vs. 941). The sensitivity and specificity of LDCT screening were 94 and 73%, respectively [20]. For comparison, the sensitivity in the chest X-ray arm was 60–70% across all 3 screening rounds. In the NLST, non-calcified nodules ≥ 4 mm or other radiological signs of lung cancer were considered positive. The rate of positive findings was high at 24.2% for LDCT as compared to 6.9% for chest X-ray. Guidelines were developed for the management of positive findings; however, these were not obligatory. Most findings could be worked up with non-invasive measures. The number of invasive procedures per diagnosed lung cancer was relatively low. Complications were rare at 1.4% in the LDCT arm and 1.6% in the chest X-ray arm. Worse complications occurred primarily in patients in whom lung cancer was diagnosed. The rate of complications in patients who underwent an invasive workup and had lung cancer was 11.2%. In comparison, serious complications in patients who underwent an invasive workup but did not have lung cancer was 0.06%.

Outside the United States (US), three European randomized controlled screening studies have so far yielded results based on a screening and a control group [21–24]. These trials were generally smaller by a factor of 10 as compared to the NLST. The risk profiles and ages of the enrolled participants also differed. Hence, a direct comparison with the NLST does not make sense. In the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays Study (DANTE Study), an annual screening with LDCT was compared with observation. Patients aged 60–74 years and with a smoking history of more than 20 pack-years were enrolled. A total of 1,276 participants were randomized. In this study, screening was also shown to be advantageous in terms of lung cancer-specific mortality and overall mortality [21, 22]. The Danish Lung Cancer Screening Trial (DLCST) was a single-center study that also compared LDCT screening with observation. Persons 50–70 years of age with more than a 20 pack-year history of smoking were enrolled, with a total of 2,052 participants randomized. In this trial, no benefit was found in the screening arm with respect to disease-specific and overall mortality [23]. Similarly, the Multicentric Italian Lung Detection (MILD) Trial was a single-center trial that enrolled younger subjects, aged 49 years and older, who had more than a 20 pack-year history of smoking. The subjects were randomized to the

LDCT screening arm or to an observation arm. This study also failed to show a difference in mortality (table 2) [24].

In summary, the NLST currently stands as the largest worldwide randomized controlled lung cancer screening study. More than 50,000 people with a defined risk profile were enrolled in this trial. LDCT screening compared to screening by chest X-ray lowered lung cancer-specific mortality by 20% and overall mortality by 6.7%. The number needed to screen (NNS) to prevent 1 lung cancer death was 320; the NNS to prevent a death overall was 219 over 6.5 years. One can compare these results with the NNS in other cancers. The NNS to prevent breast cancer death in mammography studies is 1,329 after 11–20 years of follow-up. To prevent a colorectal cancer death, the NNS by colonoscopy is 817 [25]. Thus, there are credible and valid data that make comprehensive screening by LDCT in a defined risk group a reasonable undertaking.

Lung Cancer Screening: Contra

Hans Hoffmann (Heidelberg)

Introduction

Lung cancer is the leading cause of all cancer deaths worldwide. More than 310,000 men and women in Europe will be diagnosed with lung cancer this year, more than 265,000 will die of the disease [26]. Despite the fact that lung cancer is by far the number one deadly cancer, there has never been a proven screening test for it – at least not before November 2010 when the results of the NLST were published [20, 27]. Screening for lung cancer in the NLST showed a 20% relative reduction in mortality, and 320 participants were needed to screen to prevent 1 lung cancer death. These findings were met with great enthusiasm, but before a widespread public health screening program is implemented, limitations and harms associated with screening for lung cancer also need to be considered [28].

Background

The establishment of an effective screening for lung cancer has been an elusive task for many years. Early randomized

Table 3. Low-dose computed tomography (LDCT) versus chest X-ray screening (modified from [59]); based on the National Lung Screening Trial: 53,454 current and former smokers were randomly assigned to be screened once a year for 3 years with low-dose CT or chest X-ray; these are the results after 6.5 years

Total benefit/harm of low-dose CT	LDCT	Chest X-ray
	26,722 participants	26,732 participants
Benefit		
4 in 1,000 fewer died from lung cancer	13 in 1,000	17 in 1,000
5 in 1,000 fewer died from all causes	70 in 1,000	75 in 1,000
Harm		
222 in 1,000 more had at least one false alarm	365 in 1,000	142 in 1,000
18 in 1,000 more had a false alarm leading to an invasive procedure, such as bronchoscopy, biopsy, or surgery	25 in 1,000	7 in 1,000
2 in 1,000 more had a major complication from invasive procedures	3 in 1,000	1 in 1,000

screening trials that assessed combinations of chest X-ray and sputum cytology did not show a mortality benefit from screening [29]. Chest CT screening for lung cancer has always been promising, in particular since multidetector helical CT became available which allows quick acquisition of thin overlapping slices of the entire lung within one breath hold using only a low radiation dose. Early CT screening efforts included studies initiated by the ELCAP in the US, and in Germany by a group led by Stefan Diederich of the University of Münster [17, 30]. These studies provided valuable data on screen-positive rates and estimated risk of developing lung cancer [27, 29]. However, due to the single-arm cohort design, none of the studies was designed to address the effects of LDCT screening on lung cancer mortality in an appropriate protocol [27].

Lung Cancer Screening with Low-Dose CT

The National Lung Screening Trial

In the US, the NLST enrolled 53,454 participants aged 55–74 years who were current or former heavy smokers (the equivalent of a pack per day for 30 years) at 33 US medical centers. Participants were randomized to receive either LDCT (n = 26,722) or chest X-ray (n = 26,732) annually for 3 screening rounds [20]. LDCT screening tests were considered positive and potentially related to lung cancer if they revealed at least 1 non-calcified nodule 4 mm in largest diameter (or other abnormalities suspicious for lung cancer), and chest X-ray screens were positive if they revealed any non-calcified nodule or mass. Overall, 24.2% of CT screens and 6.9% of chest X-ray screens were positive. Participants who received all 3 screens had a 39% rate of screen positivity, and 96% of these were false-positive or did not show lung cancer [20, 31]. Lung cancer-specific mortality rates were 247 per 100,000 person-years and 309 per 100,000 person-years in the LDCT and chest X-ray arms, respectively. This resulted in a 20% relative reduction in lung cancer mortality in the LDCT arm (95% confidence interval (CI) 6.8–26.7%) and an absolute risk reduction for lung cancer death by 4 per 1,000 individuals screened. The rate of death from any cause was reduced in the

LDCT arm as compared with the CXR arm by 6.7% (95% CI 1.2–13.6; p = 0.02) [20, 27]. To help doctors and patients see the key results from the NLST in an appropriate context, the US National Cancer Institute recently posted a ‘Patient and Physician Guide’ for lung cancer screening, which was designed in collaboration with the NLST Factsheet Working Group (table 3) [32]. The table shows absolute risks and risk differences for each outcome for both groups; absolute risks were used because they are less likely than relative risks to exaggerate numerically small effects [32].

European Trials

In Europe, seven randomized controlled trials of low-dose CT screening for lung cancer are underway. Recruitment has been completed in all trials, except for the UK Lung Screening (UKLS) Trial [33]. All European trials have recruited substantially fewer individuals than NLST, and only one (NELSON, the Dutch-Belgian lung cancer screening trial), which is the largest with 15,422 participants, is powered at 80% to show a reduction in lung cancer mortality of at least 25% at 10 years after randomization [33, 34]. The (Danish) DLCST has enrolled 4,104 participants [35], the (German) LUSI trial has recruited 4,052 participants [36], the (Italian) DANTE trial has enrolled 2,472 participants [22], and the ITALUNG study has randomized 3,206 participants to LDCT versus no screening, respectively [37]. Finally, the (Italian) MILD study has randomized 1,723 participants to control, 1,186 to biennial CT, and 1,190 to annual LDCT [24]. The UKLS trial has recruited into the pilot phase only [33, 38]. All European trials have in common that LDCT screening is compared with a no-screening arm, and for all trials only heavy current and former smokers have been included [39].

No reduction in deaths with CT screening has been shown in the MILD, DLSCT, and DANTE studies [23, 24, 40]. Despite more lung cancers detected in the LDCT arms and more early-stage cancers, there were similar numbers of advanced cancers compared to controls, and there was no mortality reduction with LDCT screening. However, these trials were underpowered to detect a mortality reduction of 20% as with the NLST [31]. Mortality data from the NELSON and LUSI

trials will become available in 2015. After completion of the UKLS Pilot in 2013, mortality data from this trial can be expected in 2018 [39].

Benefits and Harms of LDCT Screening for Lung Cancer

Two recent detailed systematic reviews analyzed evidence for the effectiveness and harms of LDCT screening for lung cancer: one by Bach et al. [41] on behalf of a multi-society collaborative initiative involving the American Cancer Society, the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network, and the other by Humphrey et al. [42] to update the US Preventive Task Force recommendation.

Effect on Mortality

Four randomized controlled trials have reported the impact of LDCT screening on lung cancer-specific mortality among individuals with smoking exposure, of which the NLST was considered the most informative [41, 42]. This large good-quality trial reported that screening with LDCT was associated with significant reductions in lung cancer-specific (20%) and all-cause (6.7%) mortality. Three small European trials showed no benefit of screening [42].

Effect on Smoking Habits

No studies have evaluated whether public statements regarding the benefits of LDCT screening affect smoking behavior. It has been speculated that undergoing LDCT screening may result in justification of continued smoking, or may represent an opportunity for successful smoking cessation. Studies examining the smoking behavior of LDCT-screened individuals have not found evidence that cessation or re-initiation rates are meaningfully altered by participation in screening [41].

False Alarms

LDCT identifies both malignant and benign non-calcified nodules, the latter often being called 'false positives'. Although most LDCT screening studies have reported on the nodules detected, the categorization and manner of reporting are inconsistent. Across studies, the average nodule detection rate per round of screening was 20%, but varied from 3 to 30% in randomized controlled trials and from 5 to 51% in cohort studies. Most studies reported that >90% of nodules detected were benign [41]. Most often a detected nodule triggered further imaging, but the underlying management protocols were inconsistently reported in the studies. The frequency of further CT imaging among screened individuals ranged from 1 to 44.6%. The frequency of further positron emission tomography (PET) imaging among screened individuals exhibited much less variation, ranging from 2.5 to 5.5%. The frequency of invasive evaluation of detected nodules was generally low but varied considerably [41]. In the NLST, 1.2% of patients who were not

found to have lung cancer underwent an invasive procedure such as needle biopsy or bronchoscopy, while 0.7% of patients who were not found to have lung cancer had a thoracoscopy, mediastinoscopy, or thoracotomy [43]. In the NELSON study, these numbers were 1.2 and 0.6%, respectively [34, 41].

False-Negative Findings

There is no clear definition for negative findings on screening LDCT, and sensitivity is typically determined by considering new incidents of lung cancer presenting within 1 year of a screening study as false-negative. In the 6 studies reporting this variable, sensitivity of LDCT for detecting lung cancer ranged from 80 to 100% (most often >90%), implying a false-negative rate of 0–20% [42].

Complications of Diagnostic Procedures

The only study reporting on complications resulting from LDCT screening is the NLST. Overall, the frequency of death occurring within 2 months of a diagnostic evaluation of a detected finding was 8 per 10,000 individuals screened by LDCT, and 5 per 10,000 individuals screened by chest X-ray. Some of the deaths after a diagnostic evaluation were presumably unrelated to follow-up procedures, as 1.9 and 1.5 per 10,000 occurred within 2 months when the diagnostic evaluation involved only an imaging study. Overall, the frequency of a major complication occurring during a diagnostic evaluation of a detected finding was 33 per 10,000 individuals screened by LDCT, and 10 per 10,000 individuals screened by chest X-ray. The vast majority of major complications occurred after surgical procedures, and in patients with lung cancer. The rate of major complications in those patients with lung cancer who underwent surgery was 14%. Focusing only on those patients who had nodules detected by LDCT that turned out to be benign, death occurred within 60 days among 0.06%, and major complications occurred among 0.36% [41].

Overdiagnosis

Overdiagnosis refers to histologically confirmed lung cancers identified through screening that would not impact the patient's lifespan if left untreated [41]. During follow-up, 1,089 lung cancers were reported in the LDCT arm and 969 in the chest X-ray arm of the NLST. The probability is 18.5% (95% CI 5.4–30.6%) that a lung cancer (any type) detected by screening with LDCT was an overdiagnosis, 22.5% (95% CI 9.7–34.3%) that a non-small cell lung cancer detected by LDCT was an overdiagnosis, and 78.9% (95% CI 62.2–93.5%) that a bronchioalveolar lung cancer detected by LDCT was an overdiagnosis. The number of cases of overdiagnosis found among the 320 participants needed to be screened in the NLST to prevent 1 death from lung cancer was 1.38 [28].

Radiation Exposure

The effective dose of radiation with LDCT is estimated to be 1.5 mSv per examination; however, diagnostic chest CT (ap-

proximately 8 mSv) or PET-CT (approximately 14 mSv) to further investigate detected lesions rapidly increase the exposure and account for most of the radiation exposure in screening studies. It is estimated that NLST participants received approximately 8 mSv per participant over the 3 years, including both screening and diagnostic examinations (averaged over the entire screened population) [41]. Estimates of harms from such radiation come from several official bodies and commissioned studies, based on dose extrapolations from atomic bombings and also many studies of medical imaging. Using the NLST data, these models predict approximately 1 cancer death caused by radiation from imaging per 2,500 subjects screened. Therefore, the benefit in preventing lung cancer deaths in NLST is considerably greater than the radiation risk [41].

Quality of Life

Seven studies evaluated psychosocial consequences among persons undergoing LDCT screening. In the NELSON and DLCST trials, screening did not affect overall health-related quality of life or long-term anxiety. In the short term, the studies suggested increased anxiety or distress compared with baseline among participants with positive or indeterminate results [44]. Distress and fear of cancer decreased compared with baseline among those with negative results [42].

Discussion

The US NLST has clearly changed the landscape of lung cancer screening, since it provides strong evidence that LDCT screening can reduce lung cancer-specific and all-cause mortality [20, 27]. In recognition of these results, the US Preventive Services Task Force in Lung Cancer has recently announced its support of a recommendation for CT-based lung cancer screening in 55- to 80-year-olds who have a history of 30 pack-years of smoking or of up to 15 years as an ex-smoker [45], which means that private insurers in the US will be required to cover the full costs of CT screening in this population over the next year. Moreover, all current US guidelines recommend lung cancer screening with LDCT [33]. The National Comprehensive Cancer Network (NCCN) Lung Cancer Screening Panel provided the first report after reviewing the available evidence [46] and has since updated its recommendations [47]. Further recommendations followed from the American Lung Association, the American College of Chest Physicians [29], the American Association for Thoracic Surgery [48], and the American Cancer Society [49]. Nevertheless, uncertainty exists about potential harms and the generalizability of results. These concerns should be addressed before screening becomes standard care in Germany.

Participant Selection

At present, the only population for which there is a demonstrated benefit is that defined by the NLST: smokers with at

least 30 pack-years of exposure, who are aged 55- to 74 years, and who quit less than 15 years ago. Expanding screening to cohorts other than those included in the NLST is probably not warranted at this time unless it is in the context of a research study [29]. The value of LDCT screening is determined primarily by the risk of lung cancer versus competing causes of death [41]. A recent re-evaluation of the NLST dataset that stratified participants according to their risk for lung cancer showed that the number of CT-prevented lung cancer deaths strongly increased with an increase in the pre-screening risk of death from lung cancer. Consequently, the number of participants who would need to be screened to prevent 1 lung-cancer death decreased from 5,276 among the 20% of participants at lowest risk to 161 among the 20% at highest risk. Also, the number of participants with false-positive results on screening per CT-prevented lung cancer death decreased from 1,648 among the 20% of participants at lowest risk to 65 among the 20% at highest risk [50]. Therefore, the use of an accurate model that incorporates additional risk factors to select persons for screening is likely to be cost-effective and will reduce harm to people with the least risk of lung cancer [33, 51]. Individualized risk estimation has been developed in several models [52–54]. The PLCO cancer screening trial lung cancer risk model was developed from the largest dataset known to date. A revised version of this model has recently been applied to the NLST dataset and selected 81 additional people for screening who received a diagnosis of lung cancer in follow-up, which would have resulted in 12 fewer deaths [33, 51]. In addition, one should be cautious when generalizing lung cancer screening results from the NLST to other countries with different demographics and healthcare systems. When Heuvers et al. [55] applied the NLST selection criteria to an ongoing population-based prospect cohort study in Rotterdam, the Netherlands, they found that only 29.8% of lung cancer cases that occurred in their cohort met the NLST criteria. Consequently 70.2% of cases would not have been included in a screening trial based on NLST inclusion criteria. A relative reduction in mortality from lung cancer of 20%, as shown in the NLST, would correlate with a 6% reduction in mortality in the Rotterdam study population.

Minimizing Harms

Harms associated with screening must be balanced with the benefits [42]. Concerns have been raised about potential harms from lung cancer screening, mainly in terms of potential complications from unnecessary procedures carried out to investigate what turn out to be benign, inconsequential nodules [29]. In the NLST, 4 in 1,000 fewer died from lung cancer. However, in the LDCT arm, 25 in 1,000 had a false alarm leading to an invasive procedure such as bronchoscopy, biopsy, or surgery; and 3 in 1,000 had a major complication from such invasive procedures. Predetermined algorithms for nodule assessment can minimize the number of further imaging studies or invasive biopsies to what is truly necessary. In the NELSON and UKLS trials, prespecified algorithms are used to manage indetermi-

nate nodules, rather than regarding all nodules of a specific size as positive, as done in the NLST [33]. Results from these trials will contribute important additional information that could help to better design future screening programs [33].

Overtreatment is of specific concern in lung cancer screening. The data from a recent analysis of the NLST dataset suggest that 18% of persons in the LDCT arm with screen-detected lung cancer and 22% of those in the LDCT arm with screen-detected non-small cell lung cancer may be cases of overdiagnosis. In other words, if these individuals had not entered the NLST, they would not have received a lung cancer diagnosis or treatment, at least not for the next 5 years [28]. This is most striking in patients with a diagnosis of minimally invasive adenocarcinomas, suggesting an indolent behavior and good long-term outcome. These data raise the question as to the necessity and the type of therapy required if a diagnosis of minimally invasive adenocarcinoma is established, and challenge the diagnostic community to develop a classification system that could accurately phenotype all lung tumors [28]. In a recent survey, 51% of all participants were not prepared to start a screening that results in more than 1 overtreated person per 1 life saved from death due to cancer [56]. The number of cases of overdiagnosis found among the 320 participants who would need to be screened in the NLST to prevent 1 death from lung cancer was 1.38 [28].

Implementation

As shown with the NLST, LDCT screening in a highly structured setting with tightly controlled selection can lead to a decrease in the rate of death from lung cancer. To which degree these results can be achieved if screening is implemented on a broader scale is unclear [29]. Potential harms from surgical procedures, especially for benign nodules, are a particularly prominent issue. In the NLST, the mortality from such resections was 1%, which compares favorably to that reported from specialized high-volume thoracic centers [57]. For comparison, in low-volume hospitals, mortality of major pulmonary resections is usually in the range of 3–5% [29, 57]. All major societies and organizations active in this arena in the US have issued formal statements outlining components of an appropriate lung cancer screening program. One frequent recommendation calls for the development and implementation of quality metrics to assess whether the screening processes are actually achieving the desired balance of benefits and harms [29].

In Europe, the NELSON trial and the pooling of the European randomized controlled CT screening trials will provide further mortality data on CT screening and also cost effectiveness within the European healthcare systems. These trials will also provide a deeper insight into risk stratification of the general population and a robust radiological protocol which will reduce the number of false-positives and also assist with the management decisions concerning indeterminate nodules [58]. Results from these trials will become available in 2015 to 2016.

Recently, European randomized lung cancer CT screening

(EUCT) trial investigators published a position statement with regard to the implementation of CT screening and the performance of CT screening outside clinical trials in Europe [39]. The EUCT trialists consider that CT screening is not ready for implementation in Europe at this time and that we should await the outcome of the ongoing EU screening trials in order to address the following issues: i) Identification of high-risk individuals for lung cancer CT screening programs; ii) Development of radiological guidelines for use in developing national screening programs; iii) Development of guidelines for the clinical workup of 'indeterminate nodules' resulting from CT screening programs; iv) Guidelines for pathology reporting of nodules from lung cancer CT screening programs; v) Recommendations for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programs; and vi) Integration of smoking cessation practices into future national lung cancer CT screening programs. These issues remain to be resolved before an optimal lung cancer screening program can be established within our national healthcare system.

Lung Cancer Screening: Comment

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In this issue of the journal we are witnesses to a lively pro and con discussion about lung cancer screening in Germany. Both Deppermann (pro) and Hoffmann (con) attempt to summarize the current evidence on this important issue and give their expert conclusions. Moreover, Hoffmann alludes to the EUCT investigators' position statement, and quotes their major points – his institution being part of that ambitious European initiative [39].

To be concise, we can highlight that Deppermann feels that following the NLST results 'the time is right to implement a comprehensive lung cancer screening by annual LDCT in a defined risk group' [20]. Hoffmann is considerably more cautious in his interpretation of the NLST implications: He and the other EUCT investigators propose to 'wait for the results of the NELSON randomized controlled trial in Europe and the pooling of the other European randomized controlled CT screening trials (scheduled for 2015/2016) prior to implementing CT screening in Europe in order to answer several yet unresolved questions prior to going out into the medical public with a widespread screening program [20, 34, 39].

Where shall we throw our hat into the ring following this apparent scientific deadlock? Are there significant issues not addressed by both sides? Is there a rational conclusion from both viewpoints with consequences for the current management of lung cancer screening in Germany? Here is a possible third way meant to bring together the contrary viewpoints:

- i) The first presentation and publication of the NLST results pointing out the 20% reduction in lung cancer mortality and 6.7% reduction in overall mortality dates back as far as December 2010 at the IASLC/ASCO Chicago Multidisciplinary

Symposium in Thoracic Oncology where Denise Aberle first presented the final results [60]. If we wait in Germany until the individual European datasets have been pooled, analyzed and published, and implement them into new recommendations for Germany, this would probably not happen before the end of 2016/beginning of 2017. Can we really afford to postpone the implications of such important findings for about 7 years? Who will ever count the number of lost lung cancer patients resulting from this ‘slow train coming’? [61].

- ii) Both expert statements and even the early and current NLST publications themselves may potentially underestimate the ultimate benefit of a further (even if reduced to 2-yearly) repetitive LDCT screening in this high-risk population beyond the 3 scans performed in NLST and the effects on the risk-benefit ratio of such an amendment. Although speculative and thus far without clear-cut data, the risk of further screening investigations may increase relatively slower than the benefit from detection of further diagnosed lung cancers in other participants in the years to come. This argument alone may justify the immediate start of a prospective and well-designed screening program in Germany.
- iii) None of the two opponents openly talked about the ‘grey screening’ that is and will surely be taking place in Germany based on the data published up to this point – sometimes even paid by the high-risk smokers themselves, sometimes performed based on soft parameters of ‘changes in cough history and clinical symptoms’ as documented by physicians put under pressure by their patients. Such an erratic approach to ‘screening’ may even be worse than no reaction at all but is unfortunately highly realistic. This would be the strongest argument for starting a nationwide, structured, controlled, and well-designed lung cancer screening program as soon as possible in high-risk individuals, with a rigid quality assurance program implemented for LDCT as well as a clearly predefined algorithm for handling indefinite findings both for further imaging and the performance of interventions [58, 62].
- iv) Since 2008/2009, we do have in Germany a rapidly growing number of Comprehensive Cancer Centers (certified by German Cancer Aid) as well as Lung Cancer Centers (certified by the German Cancer Society), who are more and more implementing strict quality control and assurance measures for diagnosis (bronchoscopy, CT, PET-CT, endo-

bronchial ultrasound, pathology, etc.) and therapy (surgery, radiation therapy) coupled with ongoing tumor documentation and structured follow-up. As this is not the case in many other European countries, the German setting would be perfect for such a high-level nationwide initiative. In no other country would the risk-benefit ratio be less than in such an optimized environment.

- v) Once started, this nationwide lung cancer screening program could be planned as an open platform with possible yearly or 2-yearly adjustments following major research findings from ongoing European prospective randomized trials. Nevertheless, it could only be successful if the major disciplines and their national societies worked together in the multidisciplinary steering committee of this program: the German Respiratory Society (DGP), the German Roentgen Society (DRG), the German Society for Thoracic Surgery (DGT), the German Society for Hematology and Medical Oncology (DGHO), the German Society of Radiation Oncology (DEGRO), and the German Society of Pathology (DGP), together with the major research facilities of the German Cancer Research Center (DKFZ). Important initiatives such as smoking cessation programs and prospective biomarker investigations (proteomics, molecular genetics), but also healthcare economic analyses, could be linked to this important nationwide project.

Even if lung cancer screening was to be planned for implementation as late as 2016/2017, it would still be much safer for the individual participant if it was performed in the context of such a multidisciplinary high-level program rather than on an individual basis in a setting of badly organized and quality-assured diagnostics and therapies. Time is ticking away, and therefore a nationwide initiative should be started now, rather than wasting so much precious time during which significant changes and implementations could be achieved and the pitfalls of this new technique learned in order to conquer this devastating disease with so many projected cancer deaths in the coming years!

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