Characteristics of Lung Cancers Detected by Computer Tomography Screening in the Randomized NELSON Trial

Nanda Horeweg1,2, Carlijn M. van der Aalst1, Erik Thunnissen3, Kristaia Nackaerts4, Carla Weenen5, Harry J. M. Groen6, Jan-Willem J. Lammers7, Joachim G. Aerts2, Ernst T. Scholten8, Joost van Rosmalen1, Willem Mali9, Matthijs Oudkerk10, and Harry J. de Koning1

1Department of Public Health and 3Department of Pulmonary Medicine, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; 2Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands; 4Department of Pulmonary Medicine, KU Leuven, Leuven, Belgium; 5Department of Pulmonary Medicine and 8Department of Radiology, Kennemer Gasthuis Haarlem, Haarlem, The Netherlands; 6Department of Pulmonary Medicine and 10Department of Radiology, University Medical Center (UMC) Groningen, Groningen, The Netherlands; and 7Department of Pulmonary Medicine and 9Department of Radiology, UMC Utrecht, Utrecht, The Netherlands

Rationale: The NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) trial is, with 15,822 participants, the largest European lung cancer computer tomography screening trial. A volumetry-based screening strategy, stringent criteria for a positive screening, and an increasing length of screening interval are particular features of the NELSON trial.

Objectives: To determine the effect of stringent referral criteria and increasing screening interval on the characteristics of screen-detected lung cancers, and to compare this across screening rounds, between sexes, and with other screening trials.

Methods: All NELSON participants with screen-detected lung cancer in the first three rounds were included. Lung cancer stage at diagnosis, histological subtype, and tumor localization were compared between the screening rounds, the sexes, and with other screening trials.

Measurements and Main Results: In the first three screening rounds, 200 participants were diagnosed with 209 lung cancers. Of these lung cancers, 70.8% were diagnosed at stage I and 8.1% at stage IIIB–IV, and 51.2% were adenocarcinomas. There was no significant difference in cancer stage, histology, or tumor localization across the screening rounds. Women were diagnosed at a significantly more favorable cancer stage than men. Compared with other trials, the screen-detected lung cancers of the NELSON trial were relatively more often diagnosed at stage I and less often at stage IIIB–IV.

Conclusions: Despite stringent criteria for a positive screening, an increasing length of screening interval, and few female participants, the screening strategy of the NELSON trial resulted in a favorable cancer stage distribution at diagnosis, which is essential for the effectiveness of our screening strategy.

Clinical trial registered with www.trialregister.nl (ISRCTN63545820).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung cancer is the leading cause of cancer-related death in males and the second in females globally, accounting for 1.4 million lung cancer deaths per year (1). Despite treatment advances, survival has not improved substantially, mainly because the majority of the patients have distant metastases at the time of diagnosis (2). Several randomized lung cancer screening trials were conducted with low-dose computer tomography (LDCT) scanning of high-risk groups, aiming to detect lung cancer at an earlier and curable stage (3–7).

The world’s largest randomized CT screening trial, the National Lung Screening Trial (NLST), demonstrated in 2011 that early detection by LDCT scanning has yielded a 20% lung cancer mortality reduction compared with screening by chest radiograph (8). Sixty-one percent of the LDCT-detected lung cancers were diagnosed at stage I. To accomplish this impressive result, considerable efforts were made. Namely, 26,722 high-risk subjects underwent annual LDCT screening for 3 years. Positive screening results were defined as any noncalcified pulmonary nodule measuring at least 4 mm in any diameter. In the three screening rounds, 39.1% of the individuals had at least one positive result (8).

Our trial, the Dutch–Belgian Lung Cancer Screening Trial (Nederlands-Leuvens Longkanker Screenings onderzoek; the NELSON trial), is the world’s second-largest randomized CT screening trial and differs from the NLST by screening interval, referral policy, and a control arm wherein individuals receive no screening (3). The 7,915 participants randomized to the screening...
arm of the NELSON trial underwent LDCT screening at baseline, 1 year later, 2 years later, and finally 2.5 years later. Positive screening results were defined as noncalcified nodules with a volume greater than 500 mm³ (about 9.8 mm in diameter) or volume-doubling time (VDT) less than 400 days (3, 9, 10). In the first three screening rounds, 6.0% of the participants had at least one positive screening. Clearly, the differences between the two largest randomized CT screening trials are substantial. Whether the NELSON trial will be able to demonstrate a significant lung cancer mortality reduction must be awaited, because the mortality analyses are planned 10 years after randomization (11). However, the characteristics of the screen-detected lung cancers, especially the stage distribution, might give an indication of the effectiveness of our screening strategy.

For this study, all participants with screen-detected lung cancer in the first three rounds of the NELSON trial were included. Lung cancer stage at diagnosis, histological subtype, and tumor localization were compared between the screening rounds, the sexes, and several randomized CT screening trials.

METHODS

NELSON Trial

The 15,822 individuals in the NELSON trial were randomized (1:1) to screening (n = 7,915) with LDCT at baseline (first round), 1 year later (second round), 3 years later (third round), and 5.5 years later (fourth round) or no screening (n = 7,907) (Figure 1). The main purpose of the trial is to determine whether LDCT screening will have reduced lung cancer mortality by at least 25% at 10 years of follow-up (11, 12). A more detailed report of the design and conduct was published previously (9, 11).

Participants

Individuals aged 50 to 75 years, who had smoked 15 or more cigarettes per day for 25 years or 10 or more cigarettes for 30 years and were still smoking or had quit less than 10 years ago, met the inclusion criteria. The exclusion criteria and calculation of expected lung cancer mortality were published in 2006 (11). For this study, all participants diagnosed with screen-detected lung cancer in the first three screening rounds were included (Figure 1). Hence, the interval cancers were not included in the analyses.

Equipment and Nodule Management Protocol

In short, 16-detector CT modality was used in a low-dose setting, without intravenous contrast medium (9). CT images were analyzed with software for semiautomated volume measurements (LungCARE, Siemens Healthcare, Erlangen, Germany) (13, 14).

Briefly, the screening test result could be negative (invitation for the next screen round), indeterminate (invitation for a repeat scan to determine the VDT), or positive (referral for diagnostic work-up). The nodule volume determined the screen result for newly detected nodules: less than 50 mm³ was negative, 50 to 500 mm³ was indeterminate, and more than 500 mm³ was positive. The percentage volume change was calculated for previously detected nodules: at least 25% led to the assessment of the VDT. The VDT was calculated according to the formula: VDT(days) = \(\frac{\ln 2 \times (\text{time between current scan and baseline screening})}{\ln(\text{nodule volume on current scan/volume on baseline scan})}\) (9). The screen result was positive for a VDT less than 400 days. A full description of the protocol was published previously (9, 10).

Referral and Diagnostic Work-Up

After a positive screening, the participants were referred for diagnostic work-up via their general practitioner and received usual care according to national and international guidelines (15–19). All data were prospectively collected and histological specimens were reassessed by our chief pathologist (E.T.).

Statistical Analyses

Continuous variables were tested for normality by Kolmogorov–Smirnov test for 50 or more samples and by Shapiro–Wilk test for fewer than 50 samples. Continuous, normally distributed variables were described by means and standard deviations. The difference between the means of continuous variables was calculated by one-way analysis of variance. Nonnormally distributed variables were described by medians and interquartile ranges. The difference between nominal variables was calculated by chi-square test and differences between categorical variables were calculated by Mann–Whitney U test. The difference between more than two samples of a categorical variable was calculated by Kruskal–Wallis H test. Predictors of cancer stage were tested by ordinal logistic regression; variables entered multivariate models when the P value did not exceed 0.05 univariately. P values less than 0.05 were treated as significant. SPSS Statistics version 20 (IBM, Armonk, NY) was used for all analyses.

Ethics and Legal Approval

The NELSON trial was approved by the Dutch Ministry of Health and the ethics board at each participating center. All participants gave written informed consent for participation and the evaluation of personal data from hospital charts.

RESULTS

Participants

Of the 7,915 (95.8%) participants randomized to the screening arm of the trial, 7,582 received at least one screening (Figure 1). Their baseline characteristics are presented in Table 1. The three screening rounds yielded 493 positive screen results and 200 (40.6%) participants were diagnosed with lung cancer. Synchronous double tumors were detected in four participants in
Likewise, tumor localization was not significantly different across the screen rounds: neither for the division over the lobes ($P = 0.88$) nor for the division over the peripheral versus central lung fields ($P = 0.09$).

**Effect of sex.** The women diagnosed with lung cancer were significantly younger ($58.0 \pm 62.0$ yr; $P = 0.03$), had smoked less (pack-years: $36.0 \pm 43.0$; $P = 0.03$) and had a lower BMI ($23.8 \pm 25.9$; $P = 0.03$) than the men diagnosed with lung cancer. The percentage current smokers however, was not lower in females ($56.7 \pm 55.9$%; $P = 0.93$).

None of the histological subtypes were unequally distributed between the sexes (Tables E3a and E3b). Also, the localization of the lung cancers was not significantly different between the sexes: neither for the left lung versus right lung localization ($P = 0.92$), nor for peripheral versus central localization ($P = 0.89$). However, the cancer stage at diagnosis was significantly lower in women than in men ($P = 0.005$) (Tables E3a and E3b). When correcting for the sex differences in age, number of pack-years and BMI, women still had a statistically significant lower cancer stage than men ($P = 0.028$) (Table E4).

Coincidentally, we found that a higher body mass index (BMI) (before randomization) was a significant multivariate predictor ($P = 0.004$) of a more unfavorable cancer stage at diagnosis in both sexes (Table E4).

**Comparison of trials.** A total of 1,078 lung cancers were detected by CT screening in 43,983 participants of randomized screening trials (Table 3). On average, 64.7% of the lung cancers were diagnosed at stage I and 10.9% at stage IIIb–IV (Table 3). The stage distribution in the NELSON trial appears to be relatively favorable compared with the other trials. When we compare the whole range of cancers stages between the two largest trials (NLST and NELSON) we observe that the cancer stage was significantly lower ($P < 0.001$) in the NELSON trial.

**DISCUSSION**

In this study, we have presented the characteristics of the lung cancers detected in the first three rounds of the NELSON trial. We investigated whether the screening strategy of the NELSON trial led to detection of lung cancer at a more favorable stage and how this relates to other randomized lung cancer CT screening trials.

In the three screening rounds, 493 participants had a positive screening result and were referred for diagnostic work-up. Ultimately, 200 (40.6%) participants were diagnosed with a total of 209 lung cancers. Eleven (5.5%) of these participants had symptomatic lung cancer before diagnosis; in five subjects the symptoms emerged before the screening scan was made.

More than half of the 209 screen-detected lung cancers were adenocarcinomas (51.2%) and a large majority was diagnosed at an early stage (stage I, 70.8%) (Table 2). Adenocarcinomas appeared to be diagnosed at a significantly lower cancer stage (univariate analysis $P = 0.045$), but in multivariate analysis this was no longer significant ($P = 0.56$) (Table E1). However, all bronchoalveolar carcinomas ($n = 11$) and carcinoids ($n = 6$) were diagnosed at stage I (Table 2). Four other histological subtypes were prone to be diagnosed at a higher cancer stage, for example, small cell carcinomas (multivariate analysis $P < 0.001$) (Table E1).

Most lung cancers were localized in the right lung (65.6%) and a large proportion ($45.0\%$ of all lung cancers) was localized in the periphery of lungs (Figure 3). Of the nodules, 62.2% were found in the outer one-third of the costal–hilar diameter (Figure 3). In particular, adenocarcinomas were more often detected in the periphery and attached to the pleura than in the middle or central one-third of the lungs (82.3% vs. 17.8%; $P = 0.001$). But the reverse was not true for squamous cell carcinomas (62.9% peripheral or pleural-attached vs. 57.1% central or middle one-third; $P = 0.16$).

**Effect of screen round.** The lung cancers detected in round 1 had a slightly higher disease stage (stage IA, 59.5%; stage IV, 6.8%) than in later rounds (round 2: stage IA, 74.1%; stage IV, 3.4% and round 3: stage IA, 64.9%; stage IV, 3.9%) (Tables E2a–E2c). But this was not statistically significant between rounds 1 and 2 ($P = 0.09$) or across the three rounds ($P = 0.23$).

Also, the proportion adenocarcinomas was not significantly different between rounds 1 and 2 (47.3 vs. 60.3%; $P = 0.14$) or across the three rounds (round 3, 48.1% adenocarcinomas; $P = 0.26$) (Tables E2a–E2c).

**TABLE 1. CHARACTERISTICS OF NELSON PARTICIPANTS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants</th>
<th>Participants Diagnosed with Lung Cancer</th>
<th>Participants Not Diagnosed with Lung Cancer</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), median (IQR)</td>
<td>58.0 (54.0–62.0)</td>
<td>61.0 (57.0–66.0)</td>
<td>58.0 (54.0–62.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>1,254 (16.5)</td>
<td>34 (17.0)</td>
<td>1,220 (16.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>4,215 (55.5)</td>
<td>112 (56.0)</td>
<td>4,103 (55.6)</td>
<td>0.91</td>
</tr>
<tr>
<td>Pack-years, median (IQR)</td>
<td>38.0 (29.7–49.5)</td>
<td>43.7 (32.2–75.8)</td>
<td>38.0 (29.7–49.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>25.8 (23.9–28.1)</td>
<td>25.4 (23.3–28.0)</td>
<td>25.8 (23.9–28.1)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Definition of abbreviations: BMI = body mass index; IQR = interquartile range.

* At randomization.

† In the first three screening rounds of the NELSON trial.

‡ Comparison of participants with versus without lung cancer.

round 1, in three participants in round 2, and in two participants in round 3. Thus, 200 participants were diagnosed with a total of 209 lung cancers. The patients with lung cancer were significantly older and had smoked significantly more pack-years than had the subjects not diagnosed with lung cancer (Table 1).

**Lung Cancer Symptoms**

Eleven of the 200 participants (5.5%) had symptoms suspicious of lung cancer before they were diagnosed. Five of them had symptoms before the screening scan was made; however, none of them had symptoms at randomization. Three subjects had symptoms in the period between the positive scan and the first consultation, and three subjects had symptoms in the period between the first consultation and the diagnosis date. Box plots of the time to screening result, referral, and diagnosis of the 200 participants and a detailed description of the symptoms can be found in the online supplement (Figure E1).

**Lung Cancer Characteristics**

More than half of the 209 screen-detected lung cancers were adenocarcinomas (51.2%) and a large majority was diagnosed at an early stage (stage I, 70.8%) (Table 2). Adenocarcinomas appeared to be diagnosed at a significantly lower cancer stage (univariate analysis $P = 0.045$), but in multivariate analysis this was no longer significant ($P = 0.56$) (Table E1). However, all bronchoalveolar carcinomas ($n = 11$) and carcinoids ($n = 6$) were diagnosed at stage I (Table 2). Four other histological subtypes were prone to be diagnosed at a higher cancer stage, for example, small cell carcinomas (multivariate analysis $P < 0.001$) (Table E1).

Most lung cancers were localized in the right lung (65.6%) and a large proportion (45.0% of all lung cancers) was localized in the right upper lobe (Figure 2). We also observed that the lung cancers were localized predominantly in the periphery of lungs (Figure 3). Of the nodules, 62.2% were found in the outer one-third of the costal–hilar diameter (Figure 3). In particular, adenocarcinomas were more often detected in the periphery and attached to the pleura than in the middle or central one-third of the lungs (82.3% vs. 17.8%; $P = 0.001$). But the reverse was not true for squamous cell carcinomas (62.9% peripheral or pleural-attached vs. 57.1% central or middle one-third; $P = 0.16$).

**Effect of screen round.** The lung cancers detected in round 1 had a slightly higher disease stage (stage IA, 59.5%; stage IV, 6.8%) than in later rounds (round 2: stage IA, 74.1%; stage IV, 3.4% and round 3: stage IA, 64.9%; stage IV, 3.9%) (Tables E2a–E2c). But this was not statistically significant between rounds 1 and 2 ($P = 0.09$) or across the three rounds ($P = 0.23$).

Also, the proportion adenocarcinomas was not significantly different between rounds 1 and 2 (47.3 vs. 60.3%; $P = 0.14$) or across the three rounds (round 3, 48.1% adenocarcinomas; $P = 0.26$) (Tables E2a–E2c).
TABLE 2. HISTOLOGY AND CANCER STAGE OF 209 SCREEN-DETECTED LUNG CANCERS IN 200 PARTICIPANTS

<table>
<thead>
<tr>
<th>Cancer Stage*</th>
<th>IA n (%)</th>
<th>IB n (%)</th>
<th>IIA n (%)</th>
<th>IIB n (%)</th>
<th>IIIA n (%)</th>
<th>IIB n (%)</th>
<th>IV n (%)</th>
<th>Overall n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>75 (70.1)</td>
<td>9 (8.4)</td>
<td>8 (7.5)</td>
<td>0 (0.0)</td>
<td>9 (8.4)</td>
<td>4 (3.7)</td>
<td>2 (1.9)</td>
<td>107 (51.2)</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>11 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>11 (5.3)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>21 (61.8)</td>
<td>0 (0.0)</td>
<td>3 (8.8)</td>
<td>0 (0.0)</td>
<td>8 (23.5)</td>
<td>0 (0.0)</td>
<td>2 (5.9)</td>
<td>34 (16.3)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>NSCLC–NOS</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Small/large cell carcinoma</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>5 (62.5)</td>
<td>0 (0.0)</td>
<td>3 (37.5)</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>7 (41.2)</td>
<td>1 (5.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (35.3)</td>
<td>2 (11.8)</td>
<td>1 (5.9)</td>
<td>17 (8.1)</td>
</tr>
<tr>
<td>Large cell neuroendocrine carcinoma</td>
<td>2 (50.0)</td>
<td>1 (25.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (25.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Small/large cell carcinoma</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Pleomorphic carcinoma</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>NSCLC–NOS</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>6 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>No histological diagnosis†</td>
<td>12 (92.3)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>13 (6.2)</td>
</tr>
<tr>
<td>Total</td>
<td>137 (65.6)</td>
<td>11 (5.3)</td>
<td>14 (6.7)</td>
<td>0 (0.0)</td>
<td>30 (14.4)</td>
<td>7 (3.3)</td>
<td>10 (4.8)</td>
<td>209 (100)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: NOS = not otherwise specified; NSCLC = non–small cell lung carcinoma.

*According to Reference 16.
†According to Reference 17.
‡In 13 participants no histological diagnosis was established because biopsies were unsuccessful or not performed and the patient did not undergo thoracic surgery because of poor pulmonary function (n = 7), poor heart function (n = 1), poor general condition (n = 1), metastasized prostate carcinoma (n = 1), death due to mesenteric ischemia before intended surgery (n = 1), radiotherapy because of participation in other clinical trial (n = 1), and refusal (n = 1).

The differences in lung cancer characteristics between men and women have been studied extensively. In general, studies demonstrated that women are diagnosed at an earlier age (24, 25), at a more favorable cancer stage (25–27), and are more often diagnosed with adenocarcinomas than are men (24, 28, 29). NELSON is the first trial to report on these differences in a screening setting. We also found that women were diagnosed at a significantly more favorable cancer stage than men (P = 0.028, after correction for confounding). However, the histological subtype and localization of the lung cancers were not significantly different between the sexes.

In the NELSON trial, the body mass index (BMI) was not significantly higher in the participants diagnosed with lung cancer than in participants who were not diagnosed (P = 0.09). However, a higher BMI was a significant multivariate predictor of a more unfavorable cancer stage at diagnosis (P = 0.004). This finding is in line with one other study (30). However, most studies demonstrated a negative association between BMI and lung cancer risk and prognosis (31–33). This discrepancy could be explained in the first place by reversed causation: BMI is usually measured at diagnosis, at that time weight loss has often occurred, especially patients with a higher cancer...
In the NELSON trial, BMI was measured just before randomization and because none of the participants had symptomatic lung cancer at that time, the BMI was not influenced by lung cancer itself. In the second place, the discrepancy could be explained by the strong confounding effect of smoking in many trials: smokers have a lower mean BMI than nonsmokers (34) and smoking is major risk factor for lung cancer mortality (32). This bias is probably limited in the NELSON trial because we included only (ex-)smokers (11).

In this article, we have presented an overview of the disease stage of the LDCT-detected lung cancers of the randomized screening trials. The cancer stage distribution in the NELSON trial appeared favorable relative to the other trials and was significantly lower \( (P < 0.001) \) than in the NLST. This last finding should be interpreted with caution because the NELSON trial used the 7th edition and the NLST the 6th edition of the TNM staging system (16, 35). Classification according to the 7th edition results more often in a lower cancer stage than in a higher stage compared with classification according to the 6th edition (16, 35). Consequently, this might have contributed to the lower cancer stage in the NELSON trial. Nonetheless, the NELSON trial has a number of features that could cause a higher cancer stage: first, relatively few female participants (16.5 vs. 41% in NLST), who are diagnosed at a lower stage; second, larger nodules at referral, due to relatively stringent referral criteria (nodule volume \( > 500 \text{ mm}^3 \) or nodule \( \text{VDT} > 4 \text{ mm} \) in NLST); and third, a longer screening interval (1, 2, and 2.5 yr vs. annual screening in NLST). All things considered, it seems that the NELSON strategy is at least as capable as the NLST strategy to diagnose lung cancer at a more favorable stage.

**TABLE 3. OVERVIEW OF CANCER STAGE AT DIAGNOSIS OF COMPUTED TOMOGRAPHY (CT)–DETECTED LUNG CANCERS IN RANDOMIZED CT SCREENING TRIALS**

<table>
<thead>
<tr>
<th>Trial (Ref.)</th>
<th>Participants in Screening Arm (n)</th>
<th>Screening Rounds (n)</th>
<th>Length of Screening Interval (yr)</th>
<th>Males to Females (%)</th>
<th>No. of Published CT-Detected Lung Cancers</th>
<th>Stage IA + IB Lung Cancers (n [%])</th>
<th>Stage IIIB + IV Lung Cancers [n [%]]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST (8)</td>
<td>26,722</td>
<td>3</td>
<td>1</td>
<td>59.0:41.0</td>
<td>649</td>
<td>400 (61.6)</td>
<td>130 (20.0)</td>
</tr>
<tr>
<td>NELSON</td>
<td>7,915</td>
<td>4</td>
<td>1, 2, and 2.5</td>
<td>83.5:16.5</td>
<td>209</td>
<td>148 (70.8)</td>
<td>17 (8.1)</td>
</tr>
<tr>
<td>DLST (36)</td>
<td>2,052</td>
<td>5</td>
<td>1</td>
<td>54.6:45.4</td>
<td>69</td>
<td>47 (68.1)*</td>
<td>11 (15.9)*</td>
</tr>
<tr>
<td>ITALUNG (7)</td>
<td>1,613</td>
<td>4</td>
<td>1</td>
<td>64.2:35.8</td>
<td>22</td>
<td>11 (50.0)*</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>DANTE (37)</td>
<td>1,276</td>
<td>4</td>
<td>1</td>
<td>100.0:0.0</td>
<td>58</td>
<td>41 (70.7)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>MILD (38)</td>
<td>1,190</td>
<td>10</td>
<td>1</td>
<td>68.4:31.6</td>
<td>29</td>
<td>18 (62.1)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>LUSI (39)</td>
<td>2,029</td>
<td>4</td>
<td>1</td>
<td>68.5:35.2</td>
<td>22</td>
<td>18 (81.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>43,983</td>
<td>3 to 10</td>
<td>1 to 2.5</td>
<td>65.4:34.6</td>
<td>1,078</td>
<td>697 (64.7)*</td>
<td>118 (10.9)*</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CT = computed tomography; DLST = Danish Lung Cancer Screening Trial; MILD = Multicentric Italian Lung Detection; NELSON = Nederlands Leuvens Longkanker Screenings Onderzoek (Dutch–Belgian Lung Cancer Screening Trial); NSLT = National Lung Screening Trial.

* This does not include two participants diagnosed with limited-stage small cell lung carcinoma.
† This includes the participant diagnosed with extensive-stage small lung carcinoma.
‡ This does not include the three participants diagnosed with limited-stage small cell lung carcinoma.
§ This does not include the four participants with limited-stage small cell lung carcinoma.
Naturally, this result raises a question concerning what the difference in cancer stage between the two trials would be if all lung cancers in screened participants were compared. Analysis showed no significant difference ($P = 0.21$), despite the shorter interval between screen rounds in the NLST (8).

Strengths of this study are the robust design (a large, randomized controlled trial) and prospective data collection. Limitations of this study are the lack of data for the control arm of the trial and lung cancer mortality. We have planned to perform analyses with those data 10 years after randomization, in accordance with the main purpose of our trial (11).

In conclusion, despite stringent referral criteria, an increasing length of screening interval, and a small proportion of female participants, the screening strategy of the NELSON trial resulted in a favorable cancer stage distribution at diagnosis, which is essential for the effectiveness of our screening strategy.

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank their secretary M. Quak, data manager R. M. Vernhout, and system controllers R. Faber and F. Santegeoeds for contributions and for maintenance of the database. Also, the authors thank Dr. H. Stam (lung physiologist, Erasmus Medical Center) for useful comments.

References


