EARLY DETECTION IS POSSIBLE AND SAVES LIVES

TRIAL SUMMARY: CT scan and nodule check provide model for screening programs

De Koning HJ, Van Der Aalst CM, ten Haaf K, Oudkerk M. Effects of volume CT lung cancer screening: mortality results of the NELSON randomised-controlled population based trial. Presented at WCLC, September 2018, Toronto.

The aim of the NELSON population-based randomized controlled trial is to reduce lung cancer mortality by 25% at 10-year followup using nodule volume management for referral. Of 606,409 persons aged 50 to 74 in the Netherlands and Belgium who were sent a general questionnaire about risk factors, 150,920 responded, and 30,959 were eligible and invited to participate; 15,822 gave informed consent and were randomized equally to either computerized tomography (CT) screening or no screening. Participants in the study arm received CT screening 1, 2, 4 and 6.5 years after randomization, whereas no screening was offered to control arm participants. Participants' medical records were linked to national registries of cancer diagnosis and date and cause of death. By end of 2015, 99% of participants had been followed for a minimum of 10 years.

CT screening compliance was 94% on average, leading to a total of 29,736 scans. In 9.1% of the participants, additional CT scans within 2 months were performed to estimate nodule volume doubling time, leading to an overall referral rate of 2.1% for suspicious nodules. Detection rates across the rounds varied between 0.8% and 1.0%, and 69% of screen-detected lung cancers were detected at stage IA or B. A total of 261 lung cancers (including 52 interval cancers) were detected before the 4th round of screening. In a subset of patients, surgical treatment was 3 times more prevalent in patients with lung cancer in the study arm than in control arm patients (67.7% vs 24.5%, p<0,001). In total, 934 participants have died in the control arm vs 904 in the study arm. In Dutch female study participants, the rate-ratio of dying from lung cancer was 0.73 at 10 years, and 0.58 at 9 years of followup.

The minimum 10-year followup for NELSON has been reached, and full data on incidence, mortality and cause of death are available for both arms. A (nonsignificant) 41.8% lung cancer mortality reduction has been achieved in the small subset of 2,382 Dutch women. Post-hoc analysis shows a 51.4% (p=0.04) lung cancer mortality reduction at 8 years of followup.

COMMENTARY: Smoking remains the leading risk factor for developing lung cancer. Falling lung cancer incidence is correlated with increasingly stringent tobacco legislation in developed countries, while increased tobacco consumption in developing countries is bringing a rising incidence of lung cancer in those countries.[1,2]

Diagnosis of early-stage lung cancer holds a very different prognosis than stage IV lung cancer, with chance of cure varying from 30% to 70%, depending on the stage at diagnosis.[3] Unfortunately, the majority of patients present with stage IV disease.[2] Median overall survival for stage IV lung cancer, despite therapeutic advances over the last 15 years, remains around 12 months, though this can be longer in oncogene-addicted lung cancers.[4,5,6,7,8]

Although the most important public health intervention remains reducing tobacco use and smoking cessation, screening those at highest risk of developing lung cancer is also a possible strategy to reduce the morbidity and mortality associated with lung cancer.

The US National Lung Screening Trial (NLST), reported in 2011, demonstrated a 20% reduction in lung cancer mortality in 53,434 high-risk individuals using annual CT screening over 3 years, as compared with chest radiography.[9] The incidence of lung cancer in the low-dose CT population arm was 4%. Based on these results, the US Preventive Services Task Force recommended screening based on extended NLST eligibility criteria in 2013.[10] A post-hoc analysis of the NLST data suggested that women benefit from CT screening more than men. In addition, later studies were able to incorporate information about lung nodule measurement and evolution over time to guide decisions on risk of malignancy and inform decisions about whether intervention was required.

The Pan-Canadian Early Detection of Lung Cancer (PanCan) study enrolled patients with an estimated 2% risk of lung cancer at 6 years using the PLCOm2012 risk stratification model.[11] Reporting in 2017 after 5.5 years of followup, the incidence of lung cancer was 6.5%. In 2016, screening was recommended by the Canadian Task Force on Preventative Health Care, as per the NLST population and methods. Screening through clinical trial platforms is taking place in Canada, but as yet no provincially organized lung cancer screening programs have been implemented.

Pilot data from the UK Lung Cancer Screening Trial (UKLS) were published in 2016 on 4,055 patients with a 5% risk of lung cancer at 5 years, randomized to either a single low dose CT scan or observation.[12] The rate of lung cancer detection in the CT arm of this study was 2.1%. Mortality data are still not available from the Canadian and UK studies.

NELSON is a Dutch-Belgian study originally designed for a high-risk male population, though a cohort of women was added as the study opened to recruitment.[13] Women made up 15% of the 15,792 patients randomized 1:1 between CT screening and no intervention. The NELSON trial population had at least a 15-pack-year smoking history, as compared with a 30-pack-year history in NLST. Former smokers were required to have discontinued smoking within 10 years, as opposed to 15 years in NLST.

The presentation at the 2018 World Conference on Lung Cancer showed that, in the NELSON study population, there was a larger mortality benefit from CT screening with a 26 % reduction in lung cancer mortality in men at 10 years of followup. The magnitude of benefit was even greater in women, with a 39% reduction in mortality at year 10.

The discussant, Professor John Field, estimated that if the proportion of men to women in both studies were 50:50, NLST would report an overall 18% mortality reduction at 10 years and NELSON, a 33% to 44% reduction. Strikingly, the NELSON study also demonstrated a shift in disease stage at diagnosis within the intervention arm, with 50% of cancers detected at stage Ia and 12% at stage IV, compared with 8% at stage Ia and 49% at stage IV in the control arm, and in the contemporary national cancer registry.

These data strongly support low-dose CT screening in high-risk individuals as a valuable intervention nationwide and offer the promise of a stage shift similar to what has been seen in breast cancer, and a dramatic increase in cure rate associated with treating early-stage disease in the majority of cases. Linking attendance at screening with smoking cessation programs may further reduce deaths from lung cancer.

IN BRIEF

Already known

- The US National Lung Cancer Screening Trial showed that screening using annual low-dose computerized tomography (CT) for 3 years reduces the risk of lung cancer mortality by 20% after a median 6.5 years of followup. There may be a greater benefit to screening in women than in men.
- Approximately 20% of all low-dose CTs performed in NLST had false-positive results.
- The rate of at least one complication from a diagnostic evaluation following a positive screening test was between 1.4% and 1.6%.

What this study showed

- NELSON showed that low-dose lung cancer screening reduces the risk of lung cancer mortality by 26% in men and 39% in women after 10 years of followup.
- In NELSON, 9.3% of CT scans showed false positive results. Use of nodule characteristics and a repeat CT at a short interval was used to determine the need for a diagnostic evaluation.

Next steps

- Implement nationwide low-dose CT screening in populations at high risk of lung cancer, with consideration of different screening protocols for men and women.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca Cancer J Clin.* 2018:1–31.
2. Coleman M, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the international cancer benchmarking partnership): An analysis of population-based cancer registry data. *Lancet* 2011;377:127.
3. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Proect: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2016 Jan;11(1):39–51.
4. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. *J Clin Oncol.* 2013;31: 2895–2902.

5. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *NEJM* 2016; 375:1823–33.
6. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *NEJM* 2018; 378:2078–92.
7. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *NEJM* 2009; 361:947–57.
8. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *NEJM* 2014: 371:2167–77.
9. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *NEJM* 2011; 365:395–409.
10. Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: A systematic review to update the US preventive services task force recommendation. *Ann Intern Med* 2013;159:411.
11. Tammemagi MC, Schmidt H, Martel S, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian early detection of lung cancer [PanCan] study): A single-arm, prospective study. *Lancet* 2017;18:1523–31.
12. Field JK, Duffy SW, Baldwin DR, et al. The UK lung cancer screening trial: A pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Asses* 2016;20:1–146.
13. De Koning HJ, Van Der Aalst CM, Ten Haaf K, Oudkerk M. Effects of volume CT lung cancer screening: Mortality results of the NELSON randomised controlled population based trial. Plenary session WCLC 2018, Toronto.