A Summary from the 2013World Conference on Lung Cancer

Sydney, Australia

In 2011, the U.S. National Lung Screening Trial (NLST) has demonstrated that low-dose computed tomography (LDCT) screening of high risk subjects can reduce lung cancer mortality significantly. This positive result is unique, because no other screening method or therapy has even been able to demonstrate such an impact on lung cancer mortality. After the publication of this landmark paper in the New England journal of Medicine, LDCT screening for lung cancer gained substantial attention in medical journals and at medical conferences. Recently, at the World Conference on Lung Cancer in Sydney, Australia, lung cancer screening was still prominently represented at all session types by researchers from all continents. Despite the fact that the NLST has been the only trial that demonstrated a significant impact lung cancer mortality so far, research seemed to have moved on to the questions relevant for the implementation of LDCT screening.

Dr Christine Berg, former principal investigator of the NLST, presented additional lessons and future directions of the National Lung Screening Trial.
Primarily based upon the results of the NLST, the United States Preventive Services Task Force has released a draft “B” recommendation, for lung cancer screening. This means that they concluded with moderate certainty that there was substantial net benefit for screening healthy individuals with a 30 pack-year of more history of smoking, ages 55 to 79 years of age who have smoked within the past 15 years. Dr. Berg classified this “B” recommendation as reasonable, mentioning that the criteria for whom to screen may need revision.
Next, Dr. Berg summarized a number of studies performed with data of the NLST, that can attribute to improving the yield of LDCT screening or reducing the harms. The yields of screening could be improved by improving the selection of individuals eligible for LDCT screening by; using lung cancer risk prediction models, such as the one published by Tammemagi et al., or selecting individuals at higher risk, as published by Kovalchik et al. Further, integration of effective smoking cessation programs within the screening program should lead to further reduction in smoking-related morbidity and mortality. Harms of screening could be reduced by limiting false positive screening results, which were highly prevalent in the NLST. Hence, studies were performed to identify predictors of false positive screening results, which appeared to be nodules with a diameter between 4mm and 6mm, smoking cessation and radiologists‘ interpretations.
Finally, estimates from NLST data suggest that the risk of radiation-induced lung cancer is likely to be in the range 1-10 deaths per 10,000 screened. As the observed reduction in lung cancer mortality due to LDCT screening was 31 deaths prevented per 10,000 screened, the estimated radiation-related risks are therefore considerably smaller than the observed benefit. However, the follow-up procedures could double the risk of radiation-related lung cancer. This could reduce the benefit by about 30% from 31 to about 20 lung cancer deaths per 10,000 screened. Nonetheless, the impact on life-expectancy will be smaller, because the lung cancer deaths prevented occur at a younger age than the radiation-related cancer deaths.

Prof. John Field presented the first results of the UK Lung Cancer Screening Trial (UKLS), which is population-based randomized controlled trial on LDCT screening. The UKLS is currently the only trial in the world that has used a lung cancer risk prediction model to identify eligible subjects at high risk of developing lung cancer (age 50-75, risk >5% over 5yrs). By selecting subjects at a much higher lung cancer risk than in other screening trials, prof. Field aims to prove efficacy of a more cost-efficient screening program. Since the trial is currently in follow-up and some participants were still in the 3 and 12 month phases, only results the 1991 participants who have had their baseline CT were presented. Hence, 52.4% of the participants had any pulmonary nodule with a volume 15-500mm^3, which required further imaging or work-up. Four percent had nodules measuring ≥500mm^3, which required referral for diagnostic workup. 1.6% of the participants had a prevalent lung cancer so far. 87.1% were non-small cell lung cancer and 80.6% were diagnosed at stage I or II. The Pilot UKLS is due to provide an interim report in 2014.

Dr. Henry M. Marshall presented the results of a small, but well-designed study on the effectiveness of a smoking cessation intervention embedded in a LDCT screening program.
Smokers aged 60-74years, with ≥30 pack-years of smoking history who enrolled in a LDCT screening study were randomized between the smoking cessation intervention group or the control group (Table 1). Hence, the intervention consisted of single face-to-face counselling session by a thoracic physician using motivational interview techniques, on the day of attendance for LDCT screening, plus audio cessation advice (on mp3 player), plus written quit materials. The control group received written quit materials only.
At total of fifty-four participants were randomized and the self-reported smoking cessation at 1 year, confirmed with exhaled CO measurement (ECO), was compare between the two groups. Overall, ten participants (18.6%) reported smoking cessation (five had ECO confirmation and five did not have ECO testing); two patients (3.7%, one from each group) had missing data and were assumed to be continuing smokers; the remainder reported continued smoking. There was no difference in self-reported cessation between the intervention and control groups (17.8% vs 19.2% respectively). Dr. Marshall concluded that the 18% quit rate in his study was higher than reported background rates, and that the applied smoking cessation intervention did not increase quit rates. Smokers in his study reported moderate to high levels of nicotine dependence with extensive smoking histories, and, although motivated to quit, may require more intensive assistance to support smoking cessation.

Table 1. Participant characteristics

Characteristics		Control	Intervention	p value
Sex	Women	10	10	ns
	Men	16	18	ns
Education	Up to high school	13	13	ns
	Teriary	13	15	ns
	Age, years, mean	64	63	ns
	Age started smoking, years	16	17	ns
	Cigarette consumption per day, n	23	30	0.03
	Pack years smoking, mean	61	64	ns
	FEV1 % predicted, mean	92	90	ns
	Fagerstrom nicotine dependence score, mean	4.9	5.2	ns
Baseline CT scan report	Negative	12	10	ns
	Positive	14	18	ns
Self-belief in ability to quit		3.7	3.4	ns

At the presidential symposium, Dr. Nanda Horeweg presented results of a study on the lung cancer probability of subjects with CT-detected pulmonary nodules, which was a sub-study of the Dutch-Belgian lung cancer screening trial. Objective of the study was to provide evidence-based guidelines on the management of CT detected nodules, since current guidelines are still based on the consensus-based Fleischner criteria which were published in 2005 for incidentally detected nodules.
Data of 7,155 participants of the NELSON trial with 9,681 non-calcified nodules were used and complete coverage on all lung cancer diagnoses was obtained by linkages with the national cancer registry. Analyses showed that lung cancer probability was low in subjects with a nodule volume <100mm³ (≤0.7%) or diameter <5mm (≤0.6%) Moreover, probability in these subjects was not significantly different from that in subjects without nodules (0.4%). Lung cancer probability was 0.9-5.8% for nodules with a volume 100-300mm³ or a diameter 5-10mm; the VDT further stratified the probability: 0.0-0.9% for VDTs>600days, 4.0% for VDTs 400-600days and 6.7-25.0% for VDTs<400days. Lung cancer probability was high for participants with nodule volumes ≥300mm³ (8.9-26.1%) or diameters ≥10mm (11.1-26.2%), even with long VDTs. Finally, raising the thresholds for nodule size recommended by the ACCP for an indeterminate result from 4mm to 5mm and for a positive result from 8mm to 10mm, would yield fewer follow-up CT examinations (from 29.8% to 22.2%) and fewer additional diagnostic procedures (from 8.9% to 5.3%) while maintaining the sensitivity at 94.2%.
Dr. Horeweg concluded that the lung cancer probability of individuals with small nodules (volume <100mm³ or diameter <5mm) does not justify the harms of additional scans or diagnostic procedures. In contrary, immediate diagnostic evaluation is necessary for subjects with large nodules (volume ≥300mm³ or diameter ≥10mm) and only for subjects with nodules of intermediate size is follow-up CT examinations for nodule growth assessment recommended.

Table 2 Probability of lung cancer diagnosis within two years, by diameter of largest non-calcified nodule

Max. diameter of largest nodule†	Rounds 1 and 2 Cases	Rounds 1 and 2 All	Probability of lung cancer
≥30	6	19	31·6 (15·2-54·2)***
20 - 30	22	88	25·0 (17·1-35·0)***
15 - 20	29	148	19·6 (14·0-26·8)***
10 - 15	49	442	11·1 (8·5-14·4)***
8 - 10	16	556	2·9 (1·7-4·7)***
7 - 8	12	655	1·8 (1·0-3·2)***
6 - 7	3	702	0·4 (0·1-1·3)
5 - 6	12	1,349	0·9 (0·5-1·6)*
4 - 5	4	1,575	0·3 (0·1-0·7)
<4	5	860	0·6 (0·2-1·4)
No nodule detected	30	7,630	0·4 (0·3-0·6)
All participants	188	14,024	1·3 (1·2-1·5)

† Maximum diameter of the largest nodule in a participant in mm, the interval includes the lower limit, not the upper limit. Estimates based on diameters assessed using semi-automated volumetry.
* p-value <0·05, ** p-value <0·01 ***, p-value <0·001.

Finally, Dr. Christine Berg presented the anxiously awaited results of the cost-effectiveness of LDCT screening for lung cancer. Hence, while the National Lung Screening Trial was ongoing, data on the entire screening process and cost expenditures was collected prospectively with the specific intention of performing a cost-effectiveness analysis after conclusion of the study. Costs were based on utilization rates, derived from a subset of participants selected for medical record abstraction, and Medicare reimbursements. Compared to no screening, CT screening costs $1441 per person and provided an additional 0.0217 QALYs per person; the incremental cost effectiveness ratio was $67,000 per QALY gained. Dr. Berg concluded that CT screening for lung cancer as performed in the NLST, was cost-effective under a wide range of assumptions. Whether screening outside the trial will be cost effective will depend on who is selected for screening, how screening is performed, and how screenees are subsequently managed. As lung cancer screening will need to be covered without a deductible by insurance companies upon implementation of the Patient Protection and Affordable Care Act, appropriate implementation of screening is critical.

Link to abstract book at WCLC 2013 website:
http://www.2013worldlungcancer.org/documents/WCLC2013-AbstractBook.pdf

Nanda Horeweg, MD
Department of Public Health / Department of Pulmonology
Erasmus University Medical Center,

And

James R Jett, MD
Professor of Medicine
Division of Oncology
National Jewish Health