Randomized Study on Early Detection of Lung Cancer with MSCT in Germany

Results of the First 3 Years of Follow-up After Randomization

N. Becker, PhD, E. Motsch, MD,* M.-L. Gross, MD,* A. Eigentopf, BSc,* C.P. Heussel, MD, PhD,†‡§ H. Dienemann, MD, PhD,§‖ P.A. Schnabel, MD, PhD,§¶ M. Eichinger, MD,†‡ D.-E. Optazaite, MD,†‡ M. Puderbach, MD, PhD,†‡# M. Wielpütz, MD,‡** H.-U. Kauczor, MD, PhD,‡ J. Tremper, MD,§** and S. Delorme, MD, PhD§***

*Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany; †Department of Radiology, Thoraxklinik Heidelberg, Heidelberg University, Germany; ‡Department of Diagnostic and Interventional Radiology, University of Heidelberg, Germany; §Translational Lung Research Center (TLRC) Heidelberg, German Center for Lung Research (DZL), Germany; ‖Department of Surgery, Thoraxklinik Heidelberg, Heidelberg University, Germany; ¶Institute of Pathology, University of Saarland, Homburg, Saarland, Germany; #Abt. Radiologie, Hufeland Klinikum GmbH, Bad Langensalza, Germany; and ** Department of Radiology, German Cancer Research Center, Heidelberg, Germany.

Disclosure: C.P.H is Head of Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik, Heidelberg. He is a Member of the German Center for Lung Research. He has Stada and GSK stock ownership in medical industry. He has the following patent: Method and Device for Representing the Microstructure of the Lungs. IPC8 Class: AA61B5055FI, PAN: 20080208038, Inventors: W Schreiber, U Wolf, AW Scholz, CP Heussel. He received consultation or other fees from the following organizations: Schering-Plough 2009, 2010; Pfizer 20082014; Basilea 2008, 2009, 2010; Boehringer Ingelheim 20102014; Novartis 2010, 2012; Roche 2010; Astellas 2011, 2012; Gilead 20112014; MSD 20112013; Lilly 2011; Intermune 20132014; and Fresenius 2013, 2014. He received research funding from the following organizations: Siemens 20122014; Pfizer 20122014; MeVis 2012, 2013; and Boehringer Ingelheim 2014. He receive lecture fees from the following organizations: Gilead 20082014; Essex 2008, 2009, 2010; Schering-Plough 2008, 2009, 2010; AstraZeneca 20082012; Lilly 2008, 2009, 2012; Roche 2008, 2009; MSD 20092014; Pfizer 20102014; Bracco 2010, 2011; MEDA Pharma 2011; Intermune 20112014; Chiesi 2012; Siemens 2012; Covidien 2012; Pierre Fabre 2012; Boehringer Ingelheim 2012 2013, 2014; Grifols 2012 and Novartis 2013, 2014. He has no expert testimony. He is not related to tobacco Industry. He is a Chief executive officer of the chest working group of the German Roentgen society (guidelines: bronchial carcinoma, mesothelioma, COPD, screening for bronchial carcinoma, CT and MR imaging of the chest). He is a Consultant of ECIL-3, ECCMID, EORTC (guideline for diagnosis of infections in immunocompromized hosts). He is a Founder member of the working team in infections in immunocompromized hosts of the German society of Hematology/Oncology (guideline for diagnosis of infections in immunocompromized hosts). He is a Faculty member of the European Society of Thoracic Radiology (ESTI). He is an Editor of "Medizinische Klinik, Intensivmedizin und Notfallmedizin" at Dr. Dietrich Steinkopff (Springer) publishing. The other authors declare no conflict of interest.

Funding: Deutsche Forschungsgemeinschaft, Dietmar Hopp Stiftung.

Address for correspondence: Nikolaus Becker, Division of Cancer Epidemiology, German Cancer Research Center, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany. E-mail: n.becker@dkfz.de

DOI: 10.1097/JTO.0000000000000530

ISSN: 1556-0864/15/1006-0890

Introduction: The German Lung Cancer Screening Intervention Trial (LUSI) is one of the European randomized trials investigating the efficacy of low-dose multislice computed tomography (MSCT) as a screening tool for lung cancer. In the evaluation of the first (prevalence) screening round, we observed exceptionally high early recall rates, which made the routine application of MSCT screening questionable. Because screening may behave differently in subsequent (incidence) screening rounds, we analyzed (a) basic characteristics for the annual rounds 2 to 4, which have now also been completed, and (b) the first 3 years with complete follow-up since time of randomization.

Methods: Data material was the data record of LUSI after the fourth screening round and the 3-year follow-up had been completed. Basic characteristics of screening, e.g., early recall rate, detection rate, and interval cancers as well of proportion of advanced cancers, were descriptively evaluated and, if informative, group differences were tested for statistical significance.

Results: Early recall rates were significantly lower in the subsequent screening rounds than in the first one if the MSCT information from the previous screening rounds was available. Detection and biopsy rates were approximately 1% or lower, ratio of benign:malignant biopsies: 1:1.6 to 1:3.

Conclusion: Our recent data may not only settle one concern regarding high recall rates in routine MSCT screening but also indicate that screening must be strictly organized to be effective. Performance indicators are similar to those in mammography screening. Nevertheless, possible consequences for the participants (diagnostic workup of suspicious findings, biopsies) are more invasive than in mammography screening.

Key Words: cancer, low-dose CT, lung, randomized trial, screening.

(*J Thorac Oncol.* 2015;10: 890–896)

Several randomized trials investigating the effectiveness of lung cancer screening with multislice computed tomography (MSCT) are under way in the United States[1] and Europe (reviewed in Refs. 2–8) from which the American National Lung Screening Trial having provided first results.

One of the European trials is the German *Lu*ng Cancer *S*creening *I*ntervention Trial (LUSI), which started in 2007 with 4052 study participants. One key result of its first screening round was the high early recall rate of approximately 20%

early recalls because of suspicious MSCT findings. Most of these were false-positive, which would make MSCT screening questionable for a routine program.[9] However, because screening may behave rather differently in the first (prevalence) screening round and subsequent (incidence) rounds, we analyzed the data of the subsequent rounds of LUSI with particular attention to the basic performance indicators of screening, such as early recall rate, detection rate, and interval cancer rate.

Because all participants have gone through at least 3 years of observation since randomization and many participants have gone through even 5 years or more of observation at the time of this evaluation, further indicators of the progress of this trial, such as false-positive and detection rates, interval cancers (invasive cancers diagnosed in an attender after a negative screen and before the next invitation to screening was due[10]), development of cumulative advanced incidence, or overall mortality in the study arms, can now be presented descriptively. They are partially indicative for the quality of the trial itself (advanced cancer incidence and overall mortality shortly after randomization) and partially early surrogates for the later mortality outcome of the trial (cumulative advanced cancer incidence rate).

MATERIAL AND METHODS

Data Material

The German LUSI trial is an epidemiological study among 50–69 years old males and females with a history of heavy smoking (at least 25 years smoking of at least 15 cigarettes per day or at least 30 years smoking of at least 10 cigarettes per day) randomized into a screening intervention arm, comprising a MSCT at time of randomization and four subsequent annual MSCTs, and a control arm with no intervention. Recruitment was population based from a random sample of the population registers in the area around Heidelberg yielding 4052 participants (2029 screenees and 2023 controls). Follow-up is being conducted actively by annual questionnaire mailing and passively by repeated linkage to the local population registers and cancer registries. Randomization started at October 23, 2007 and ended at April 11, 2011. A detailed description of study design was given by Becker et al.[9]

In the present evaluation, the data describing the status of the trial at April 30, 2014 were used, comprising the first four completed screening rounds. Partially, we refer to data from the fifth round, which has also been completed for about two-third of the participants by this time. For evaluations in terms of events (e.g., lung cancer diagnosis, death) by time since randomization, complete follow-up data are available for at least 3 years since randomization (for those who were randomized in April 2011) and up to 6.5 years (for those who were randomized in October 2007). The data on incident lung cancers were obtained for the screening group from the annual MSCT scans, and in the control group from the annual questionnaire inquiries followed by data collection from the treating physicians in case of self-reported lung cancer diagnoses. In addition, a linkage with the local cancer registry of Baden-Württemberg and the local population registries was carried out. Partially, we also describe also the already available data on incident lung cancers or deaths from any cause for those years (3–6.5 years of observation) for which follow-up is still incomplete.

MSCT Evaluation Algorithm

All MSCT datasets were subject to a dedicated post-processing server for computer-aided detection and nodule volumetry (Median Software, France). A key issue of the evaluation algorithm is the distinction between newly observed and previously identified nodules (Table 1). MSCTs with no nodules or nodules below 5 mm in diameter were considered negative implying continuation of routine screening after 12 months.

Newly observed nodules (Table 1, left column): All other newly observed nodules were classified as suspicious implying early recall depending on size of the largest observed nodule: Reinvitation with repeat MSCT after 6 months (largest nodule 5–7 mm in diameter), 3 months (8–10 mm), or immediate pulmonologist referral for workup (larger than 10 mm, respectively).

Known nodules (Table 1, right column): Nodules known from the previous screening round or especially the repeat MSCTs of the early recalls were first checked whether they

TABLE 1. MSCT Evaluation Algorithm Applied in the German Randomized Lung Cancer Screening Trial LUSI

Newly Observed Nodules (First Screening Round or New in Subsequent Rounds)		Known Nodules (Early Recalls or Subsequent Screening Rounds)	
Outcome by Nodule Size	**Action**	**Outcome by Nodule Growth**	**Action**
Without abnormality or nodules <5 mm	Back to routine screening (12 months)		
Nodules 5–7 mm	Early recall (6 months)	>600 VDT	Back to routine screening
		400–600 VDT	
		< 7.5 mm	Early recall (6 months)
		≥ 7.5–10 mm	Early recall (3 months)
		≤400 VDT or > 10 mm	Immediate recall
		Nonmalignant	Back to routine screening
Nodules 8–10 mm	Early recall (3 months)	Malignant	Treatment
Nodules >10 mm/not highly suspicious	Early recall (3 months)		
Highly suspicious	Immediate recall		

MSCT, multislice computed tomography; LUSI, lung cancer screening intervention trail; VDT, volume doubling time.