PhD thesis

The efficacy of lung cancer screening with low dose computed tomography

Anna Kerpel-Fronius, MD

Károly Rácz Doctoral School of Clinical Medicine

Pulmonology

Semmelweis University

Supervisor: Krisztina Bogos, MD PhD

Official reviewers: Zalán Szántó, MD PhD

Ádám Tárnoki,MD PhD

Head of the Complex Examination Committee:

Dávid Tárnoki, MD PhD

Members of the Complex Examination Committee:

Noémi Eszes, MD PhD and Sándor Manninger, MD PhD

Budapest

2022

List of Contents

1. Introduction

Lung cancer causes 1,7 million deaths annually, in Hungary, around 7000 new patients are being diagnosed every year. Primary- (i.e. smoking cessation) and secondary (i.e. population-based screening) prevention programs are needed to reduce both the incidence and mortality of lung cancer. Notably, if lung cancer is symptomatic, the disease is already locally advanced or metastatic. To date, the only curative-intent measure is the surgical removal of the tumor, but without early detection, surgical resection is only feasible in 15-25% of the cases .

The U.S.-based National Lung Cancer Screening Trial (NLST) was launched in 2002 as a control-armed, prospective trial with the ultimate goal to determine whether LDCT screening has a beneficial effect in reducing lung cancer mortality. Between 2002 and 2004, 53,454 individuals with a calculated high risk for lung cancer (55-74 years of age, smokers with 30 PYs or former smokers, who quit smoking in the last 10 years) were assigned randomly to either annual chest X-rays (CXR) or 3 annual rounds of LDCT screening. The follow-up data collection for lung cancer morbidity and mortality was continued until the end of 2009. With an adherence rate of 90%, 39.1% of the participants in the LDCT-, and 16.19% of the individuals in the CXR arm had at least one positive screening result. Of note, however, the majority of these

screening results were later classified as false positive outcomes (96.4% in the LDCT and 94.5% in the CXR arm). The high number of false positive results were due to the initial trial set-up: every non-calcified nodule with any diameter >4 mm was considered as positive. This naturally resulted in a high number of follow-up procedures, including PET/CT, bronchoscopy, transthoracic and transbronchial biopsies, and surgery

Importantly, 645 lung cancers cases were detected in 100.000 person years in the LDCT arm, whereas only 572/100.000 person years in the CXR arm. Mortality was 247/100,000 person years in participants who underwent LDCT, and 309/100,000 person years in the CXR arm (resulting in a 20% mortality decrease in the LDCT arm). These data were so convincing that in December 2013, the United States Preventive Services Task Force (USPSTF) has recommended LDCT lung cancer screening to all individuals aged between 55-80 years with a smoking history of at least 30 PYs who are active smokers, or quit smoking in the last 15 years as B grade European Screening studies and the European position statement

The largest European lung cancer screening study to date is the Dutch-Belgian Randomized Lung Cancer Screening Trial (also known as the NELSON trial). The NELSON trial was conducted in the Netherlands and Belgium, and enrolled 15,792 high-risk subjects in a LDCT screening arm or control arm with no active screening. Of note, chest X-rays are not part of the standard-of-care in asymptomatic individuals in

the participating countries. All enrolled patients were aged between 50–75 years and had a smoking history of at least 30 PY (or were former smokers with 10 years or less of cessation). LDCT screening was performed at baseline, and at 1, 3, and 5.5 years after enrollment. In addition to positive and negative screening results, a new category concerning indeterminate screening outomes was also introduced. Importantly, all individuals with indeterminate results were re-examined after 3 months, and the volume doubling time (VDT) of the nodule was measured semi-automatically. Lesions were classified as growing nodules when their growth rate was >25%. All cases where the VDT was less than 400 days were considered as positive. Although the final results are not published as of date, preliminary study results were presented at the 2018 World Conference on Lung Cancer. Specifically, a 26% mortality reduction rate was detected at 10 years of follow-up in high-risk males, and although women participated at a smaller number, their mortality benefit was even larger (39-61% at different time points). With regard to screening results, 86% and 69% of lung cancers detected were stage IA and IB, respectively. Importantly, by implementing the "indeterminate" outcome category, the number of false positive cases was greatly reduced. Specifically, while in the NLST only 3.6% of positive cases were indeed malignant lesions, in the NELSON trial the true positivity rate was 40.6%.

In 2015, the European Respiratory Society and the European Society of Radiologists published a joint ERS/ESR statement. This was followed by

the European position statement on lung cancer screening in 2017. This latter reviewed the major lung cancer screening programs to date and devised a 9-point recommendation for future lung cancer screening projects. According to these recommendations, further risk stratification models should be implemented in order to accurately select the high-risk individuals who benefit the most from screening. Patients should be advised on the harms and benefits of screening, and all active smokers should get smoking cessation counselling offered. Nodule growth should be measured by semiautomatic volume measurements.

In order to eradicate pulmonary tuberculosis, starting from 1946, annual screening was mandatory for all Hungarians over the age of 14. As the number of tuberculosis cases decreased by 2004, the annual chest X-ray screenings have become mandatory only in high-risk groups and certain professions. However, individuals over 40 years of age may participate in a so called “lung-screen” CXR free of charge. According to Korányi Bulletin, these screening CXRs diagnose approximaelly 1000 asymptomatic lung cancer patients each year. In a project conducted by Moizs and her colleagues in Kaposvár between 2012 and 2013, individuals participating in this CXR screening program were asked to fill out a questionnaire, and those who were determined to be high risk were offered LDCT if the CXR was read as negative. The main objective of this study was to characterize the people's willingness to voluntarily participate in lung screening. Moreover, this was the first study to

introduce the basic CT concepts of lung cancer screening in the Hungarian radiology practice.

2. Objectives

The main objective of the HUNCHEST trial was to determine whether a multicentre LDCT screening program is feasible in Hungary and if so, are the results comparable to those of the major international trials (such as NLST and NELSON). The question of whether the at-risk participants can be further subclassified into different risk groups is also a major scientific and a public health question dilemma. Therefore, subgroups with different smoking habits and lung status were also studied. Furthermore, due to the large- scale patient involvement, it was also necessary to create a web-based structured reporting platform.

3. Methods

The HUNCHEST pilot project was conducted as a prospective, multicenter, nationwide lung cancer screening trial. The trial design was in accordance with the guidelines of the Helsinki Declaration (as revised in 2013) of the World Medical Association. Approval was obtained from the national level ethics committee (Hungarian Scientific and Research Ethics Committee of the Medical Research Council, ETT-TUKEB, 002524–005/2014/OTIG) and also from the institutional review boards of all participating institutions. Written informed consent was acquired from all study participants involved. The primary aim of the

HUNCHEST screening program was to evaluate the efficiency of LDCT in lung cancer detection in an asymptomatic population irrespective of any known risk factors. The secondary aim was to establish the clinical pathways to assure adequate medical care in case of radiologically suspicious (or initially indeterminate) nodules to reduce cause-specific mortality.

The organizing center was The National Korányi Institute for Pulmonology, where the first part of the screening program was based. In the second part of the trial, 5 additional health-care providers joined the screening, namely Affidea Budapest Nyírő Gyula Hospital, Affidea Budapest Margit Hospital, Affidea Debrecen, Affidea Győr and Affidea Szeged. Each center was given the freedom to choose its process of recruitment, nevertheless, participation was voluntary. In the present study, all participants went through the first screening round between October 2014 and January 2020. Asymptomatic male and female individuals, between 50-79 years of age with or without known risk factors were included. Smoking cessation counseling was offered to all participants with a smoking history (including ex-smokers) at the time of recruitment. Exclusion criteria were in accordance with the NELSON trial and the current study protocol. Accordingly, people with self-reported moderate or bad health (i.e., participants who required permanent oxygen therapy), bodyweight of 140 kg or more, current or past renal cancer, melanoma, breast cancer or lung cancer diagnosed less

than 5 years ago, previous lung surgery or a chest CT examination less than 2 years ago were excluded. Since written informed consent was required, individuals who were unable to give written consent due to any condition were as well excluded. According to their smoking habits and comorbidities, participants were classified into one of the four categories: (*i*) non-smokers (adults who have smoked less than 100 cigarettes in their lifetime) or former smokers (people who had quit smoking within 10 years) diagnosed with COPD as comorbidity, (*ii*) non-smokers or former smokers without COPD, (*iii*) current smokers (adults with a history of cigarette smoking of 40 PYs or more) with known COPD, (*iv*) current smokers without COPD. All participants signed the informed consent on a voluntary basis, and were allowed to withdraw such a consent at any point of the study.

Three rounds of LDCT screening were offered to each participant with intervals of 1 year between procedures. The date of the initial screening round was discussed personally with the participant, while the follow-up rounds were decided via email. Preceding each round, all applicants underwent lung function tests (i.e., spirometry) in order to detect previously unknown COPD. All obtained scans were non-enhanced (i.e., without administration of contrast medium). Thoracic CT images were obtained during suspended maximal inspiration, in a single breath-hold, craniocaudally from lung apices to bases, with the field of view covering the whole lungs in a low-dose setting (120 kV, 20 mAs). Reconstruction was performed in overlapping contiguous in 1- and 5-mm increments. To

keep exposure to radiation as low as reasonably achievable, exposure factors were tailored to the patient's height and weight, with the aim of ensuring that the average $CTDI_{vol}$ was kept around 1.5 mGy. To optimize diagnostic accuracy, all CT scans were read by at least two independent radiologists (with experience in thoracic CTs ranging from 5 years to more than 20 years). Semiautomatic nodule segmentation and determination of the nodule volume were included in the analysis. In case of the software not being able to segment a nodule accurately, radiologists manually measured the size of the nodules. A third, senior radiologist was also involved in case of discordance between the findings. Participants were informed about the screening results once consensus had been achieved for all nodules. For subsequent LDCTs, nodules previously detected were individually matched on the archived scans. A software calculated the VDT, defined as the number of days in which the nodule doubles in volume. Of note, VDT is a theoretical number, which was devised to better estimate the growth of small nodules. Slow growing nodules with VDT >600 days are most likely benign entities. On the other hand, suspicious nodules grow more rapidly and have a VDT of <400 days. It is important to point out however that very rapidly growing nodules with a VDT of <40 days are considered likely inflammatory, and are followed up accordingly. Nodules with VDTs between 400 and 600 days are categorized as indeterminate and further radiological check-up is indicated.

4. Results

A total of 1890 participants were included in the HUNCHEST study. Among them, 819 (43.3%) participants were male and 1071 (56.7%) were female (Table 1). At enrollment, the mean age was 63.2 ± 4.7 years. The proportion of current smokers was 54.0% (n=1020), with a non-significantly higher proportion in women (p=0.192;). 18.6% (n=351) of the enrolled participants had known (or were diagnosed during the initial check-up with) COPD, which constituted the most important comorbidity.

At baseline, the percentage of negative, indeterminate and positive tests was 81.2%, 15.1% and 3.7%, respectively. Following the baseline scan patients with positive outcomes were referred immediately to the multidisciplinary team (MDT) assessment. In total, 29 lung cancers were diagnosed, thus the overall PPV of the positive screening tests was 31.6%. This means that 63 participants over all rounds had a false positive test (68.4% of total positives). In the first screening round, 1.2% of the participants had a malignant lesion, whereas altogether 1.5% of the individuals were diagnosed with lung cancer regardless of screening rounds. Importantly, however, from the initially test-negative participants, malignant lesions were detected only in two patients. Likewise, in the initially indeterminate subgroup, in total four patients were diagnosed with lung cancer, whereas 16 with benign lesions. Of

note, in case of 7 individuals, the final histopathological diagnosis was not available due to patient withdrawal. Histologically, most lung cancers were adenocarcinomas (ADCs) or squamous cell carcinomas (SCCs) followed by small cell lung cancer (SCLC) [18 vs. 7 vs. 2, respectively]. Most lung malignancies were diagnosed at stage I, II and IIIA (86.2% of total lung cancers). No statistically significant differences in age, gender, smoking status, COPD were observed between patients with benign vs. malignant lesions. Reflecting the early stage, 25 of 29 subjects had lung resection surgery (with or without adjuvant chemo- and/or radiotherapy) as their primary treatment.

5. Conclusion

HUNCHEST, which was designed as an early detection LDCT lung cancer screening program, has proven that population-based screening programs are indeed feasible within the Hungarian healthcare system. The pilot project provided valuable insights into the financial aspects of such screening programs suggesting that they can be both cost saving and cost-effective in the appropriate risk groups. Although a relatively large number of lung cancer patients diagnosed within the framework of HUNCHEST were never-smokers, our results suggest that screening is not cost-effective in non-smoker individuals.

HUNCHEST was conducted in accordance with the NELSON study protocol. Accordingly, besides classifying the screening outcomes in two categories (i.e., positive/negative) solely, a third category (i.e.,

indeterminate) was also implemented. This new, optimized nodule management protocol allowed us to reduce the number of false-positive screening results and thus to disencumber the clinicians. A web-based structured reporting platform was also devised for the project, which proved to be invaluable when comparing the results among the different health-care providers.

A group of never smoker individuals were also included in our trial, moreover we also assessed the impact of COPD on screening outcomes. To the best of our knowledge, HUNCHEST is among the first screening programs to evaluate the efficacy of LDCT screening in Caucasian never-smoker participants with regard to COPD. Importantly, in terms of key characteristics, our trial appears consistent to that of comparable studies, and the detection rate of lung cancer also lies within the range of the previous trials. Our results justify the implementation of HUNCHEST-2, which aims to examine the efficacy of LDCT screening in a large cohort of current- or former smoker participants with complete long-term follow-up data in order to reduce lung cancer mortality, and, moreover, to identify individuals who are at high risk of developing lung cancer. This later study is an ongoing nationwide implementation trial which might provide a rich resource to address the remaining questions and allow adequate early diagnosis.

6. Bibliography of the candidate's publications

6.1. List of publications that served as a basis for the current thesis

Kerpel-Fronius A, Monostori Z, Kovacs G, Ostoros G, Horvath I, Solymosi D, Pipek O, Szatmari F, Kovacs A, Markoczy Z, Rojkó L, Renyi-Vamos F, Hoetzenecker K, Bogos K, Megyesfalvi Z, Dome B. Nationwide lung cancer screening with low-dose computed tomography: implementation and first results of the HUNCHEST screening program EuRadiol 2022 doi 10.1007 330.2022.8589-7

IF: 5.315

Kerpel-Fronius A, Monostori Z, Solymosi D, Markóczy Z, Rojkó L,Kovács G. Kezdeti tapasztalatok a HUNCHEST - alacsony dózisú CT-tüdőrákszűrési pilotprogrammal Orvosi Hetilap 2018. 159. évf. 43. sz., p. 1741-1746.

IF: 0.564

6.2. Other publications

Kerpel-Fronius A, Tammemägi M, Cavic M, Henschke C, Jiang L, Kazerooni E, Lee CT, Ventura L, Yang D, Lam S, Huber RM; members of the Diagnostics Working Group; ED and Screening Committee. Screening for Lung Cancer in Individuals Who Never Smoked: An International Association for the Study of Lung Cancer Early Detection and Screening Committee Report. J Thorac Oncol. 2022 Jan;17(1):56-66. doi: 10.1016/j.jtho.2021.07.031. Epub 2021 Aug 27. PMID: 34455065.

IF: 15,609

Huber RM, Cavic M, Kerpel-Fronius A, Viola L, Field J, Jiang L, Kazerooni EA, Koegelenberg CFN, Mohan A, Sales Dos Santos R, Ventura L, Wynes M, Yang D, Zulueta J, Lee CT, Tammemägi MC, Henschke CI, Lam S; members of the Diagnostics Working Group; Early Detection and Screening Committee. Lung Cancer Screening Considerations During Respiratory Infection Outbreaks, Epidemics or Pandemics: An International Association for the Study of Lung Cancer Early Detection and Screening Committee Report. J Thorac Oncol. 2022 Feb;17(2):228-238. doi: 10.1016/j.jtho.2021.11.008. Epub 2021 Dec 3. PMID: 34864164; PMCID: PMC8639478.

IF: 15,609

Bogos K, Kiss Z, Kerpel Fronius A, Temesi G, Elek J, Madurka I, Cselkó Z, Csányi P, Abonyi-Tóth Z, Rokszin G, Barcza Z, Moldvay J. Different Trends in Excess Mortality in a Central European Country Compared to Main European Regions in the Year of the COVID-19 Pandemic (2020): a Hungarian Analysis. Pathol Oncol Res. 2021 Apr 13;27:1609774. doi: 10.3389/pore.2021.1609774. PMID: 34257618; PMCID: PMC8262208.

I: 3,201

Pako J, Bikov A, Barta I, Matsueda H, Puskas R, Galffy G, Kerpel-Fronius A, Antus B, Horvath I. Assessment of the circulating klotho protein in lung cancer patients. Pathol Oncol Res. 2020 Jan;26(1):233-238. doi: 10.1007/s12253-018-0441-5. Epub 2018 Jun 12. PMID: 29948618.

IF: 3,201

Nagy B, Szilbehorn L, Kerpel-Fronius A, Moizs M, Bajzik G, Vokó Z. A kis dózisú komputertomográfiával történő tüdőrákszűrés költségvetési hatása [The budget impact of lung cancer screening with low-dose computed tomography]. Orv Hetil. 2021 Jun 13;162(24):952-959. Hungarian. doi: 10.1556/650.2021.32095. PMID: 34120101.

IF: 0,504

Vokó Z, Barra M, Molnár A, Kerpel-Fronius A, Bajzik G, Horváth I, Moizs M, Nagy B. Az alacsony dózisú CT-vel végzett tüdőrákszűrés magyarországi egészség-gazdaságtani elemzésének koncepcionális terve [Model concept of the health economic evaluation of low-dose CT lung cancer screening in Hungary]. Orv Hetil. 2017 Jun;158(25):963-975. Hungarian. doi: 10.1556/650.2017.30731. PMID: 28627945.

IF: 0,322

Kerpel-Fronius A: Javaslat a COVID-19-fertőzésen átesett betegek mellkasi radiológiai utánkövetésére. Magyar Radiológia Online 2021; 12(1): 7.

Kerpel-Fronius A, Solymosi D: A COVID-19 okozta pneumónia képalkotása – kezdeti tapasztalataink Magyar Radiológia Online 2020; 11(2)

Kerpel-Fronius A: Első tapasztalataink a COVID-19 fertőzött betegek mellkasröntgen vizsgálatai kapcsán. MedThorac 2020 73(3) 200-204

Kerpel-Fronius A, Monostori Z: Korszerű képalkotás: ami nem látszik a spirometrián COPD-ben. OTSz, 2015. 22(11) 14-17. old.

Bohács A, Karlócai K, Kerpel-Fronius A: Az idiopathiás pulmonalis fibrosis (IPF) korszerű diagnosztikája. 3. rész. Multidiszciplinaritás és pulmonalis hypertonia idiopathiás tüdőfibrosisban LAM Lege Artis Medicinae, 2018. (28. évf.) 8-9. sz. 377-382. old.

Horváth I, Kerpel-Fronius A, Harkó T: Az idiopathiás pulmonaris fibrosis (IPF) korszerű diagnosztikája. 2. részLAM Lege Artis Medicinae, 2018. (28. évf.) 6-7. sz. 301-307. old.

Zsiray M, Kerpel-Fronius A, Fillinger J, Monostori Z, Harkó T, Gajdócsi R, Horváth KH, Horváth I.: Klinikai megfigyelések szervülő pneumoniában MedThorac 2020 73(4) 249-253

Zsiray M, Kerpel-Fronius A: Tüdőfibrosis és emphysema osszetett tünetegyüttese MedThorac 2018 71(4) 256-259

Harkó T, Szilágyi R, Vadász P, Kerpel-Fronius A, Soltész I, Kerényi AM, Fillinger J: Ismeretlen eredetű féloldali mellkasi folyadékképződés, mint a sarcoidosis ritka megjelenési formája MedThorac 2020 73(3) 209-211

Zsiray M, Kerpel-Fronius, Fillinger J, Monostori Z, Harkó T, Gajdócsi R, Horváth KH, Horváth I: ILD team a tüdőfibrózisok multidiszciplináris diagnosztikája MedThorac 2020 73(5) 326-330

Varga JT, Kerpel-Fronius A, Madurka I et al: COVID-19-világjárvány: a fertőzés lefolyása és a gyógyszerkutatások reménykeltő eredményei OTSz 2021 28(2) 87-94

Tóth G, Kerpel-Fronius A, Járay B: Férfi emlő invasiv ductalis carcinomája. Magy Radiol 1999; 73:26-8.

Galgóczy H. Tarján Z, Kerpel-Fronius A: Az ultrahangvizsgálat szerepe az emlődaganatok korszerű diagnosztikájában. Magy Radiol. 1998. 72. 4. sz.

Guidelines:

Gödény M, Kerpel-Fronius A, Bágyi P, Berényi E, Bogner P, Faluhelyi N, Kincses Zs, Maurovich Horvat P, Várkonyi I, Lombay B, Bogos K, Az Emberi Erőforrások Minisztériuma egészségügyi szakmai irányelve a képalkotó vizsgálatok alkalmazásáról a COVID-19 megbetegedés különböző fázisaiban EGÉSZSÉGÜGYI KÖZLÖNY 71: 22 pp. 2243-2285., 43 p. (2021)

Bookchapters:

Monostori Z, Kerpel-Fronius A, Soltész I, Harkó T, Zsiray M, Simon B, KormosT Esetbemutatások: klinikum, radiológia és patológia In: Tárnoki, Dávid; Tárnoki, Ádám; Karlinger, Kinga; Monostori, Zsuzsanna (szerk.) Az interstitialis tüdőbetegségek képalkotása multidiszciplináris kitekintéssel Budapest, Magyarország : Medicina Könyvkiadó (2020) 228 p. pp. 141-150. , 10 p.

Riedl E, Kerpel-Fronius A, Geszler J, Borbély K, Bell B: Komputertomográfia Budapest, Magyarország: Akadémiai Kiadó (2020) ISBN: 9789634545231