PhD thesis

The efficacy of lung cancer screening with low dose computed tomography

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1. List of abbreviations

ADC	adenocarcinoma
CAD	Computer-Aided Detection
CXR	chest X-ray
COPD	Chronic obstructive pulmonary disease
CTDI	CT dose index
HU	Hounsfield units
HUNCHEST	Hungarian LDCT Lung Cancer Screening program
I-ELCAP	International Early Lung Cancer Action Program
LDCT	low-dose computed tomography
MDT	Multidisciplinary team
MILD	Multicentric Italian Lung Detection
mGy	milligray
mSv	millisievert
NCCN	National Comprehensive Cancer Network
NELSON	Nederlands–Leuvens Longkanker Screenings Onderzoek
NLST	National Lung Screening Trial (U.S.)
PET/CT	positron emission tomography/ computed tomography
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer screening trial
PPV	Positive predictive value
SCC	squamous cell carcinoma
SCLC	small cell lung cancer
USPSTF	United States Preventive Services Task Force
UKLST	UK Lung Cancer RCT Pilot Screening Trial
VDT	Volume doubling time

2. Introduction

In 1912, Isaac Adler published a review of all lung cancer patients he could identify in the scientific literature and found a total of 374 cases [1].Nowadays, this devastating disease is the leading cause of cancer-related deaths worldwide (1,7 million deaths annually) causing more deaths than breast, colorectal, and cervical cancers combined. In Hungary, around 7000 new patients are being diagnosed every year. This substantial change in lung cancer incidence was due to the advent of modern cigarette manufacturing since smoking constitutes the biggest risk factor for lung cancer [2]. Therefore, 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 [3].

2.1. Early lung cancer screening projects

Starting in the late 1950s, lung cancer screening was a major public health issue. Importantly, all screening programs should adhere to the Wilson-Junger principles published by the World Health Organization (WHO) in 1968, which states that screening should detect a disease in an early stage, when treatment options are significantly better compared to those without screening [4]. As chest X-rays were widely available, the first studies focused on conventional radiography in a screening setting. Early non-controlled trials (such as the American Cancer Society's and Veterans Administration’s joint trial) have not been able to prove the survival benefits [5]. In the 1960s, several controlled trials were conducted (the Czechoslovakian and the Mayo Lung Project) using chest X-rays, or sputum cytology (the Johns Hopkins trial) [6]. The last major trial utilizing chest X-ray as a screening method was the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial, which included and followed up more than 150,000 individuals over 13 years, and despite finding more stage I disease, they were not able to show a reduction in mortality [7].

ELCAP and I-ELCAP trials

Due to technological advances in the field of medical imaging, screening programs started to focus more and more on computer tomography (CT). In 1992, the Early Lung Cancer Action Project (ELCAP) was launched. In total, 1000 people >60 years of age, with a smoking history of at least 10 pack years (PY) were invited to undergo low dose, non-contrast CT scanning (LDCT), as well as chest X-ray. Between 1993 and 2003, the study gained international aspects (I-ELCAP), which increased the screening pool to 31,567 asymptomatic individuals. Totally, 484 patients were diagnosed with lung cancer (out of which 85% with stage I disease). 88% of these patients had a survival rate of >10 years [8]. The study however had its own flaws. Specifically, no control arm was used, so only the efficacy of LDCT screening could be demonstrated, while the disease specific mortality rates could not be assessed. In 2008, it was revealed that key players from the tobacco industry, thus casting further shadows on the results themselves, founded some of the trials. Despite these controversies, this was the first large-scale screening program which demonstrated that LDCT might be a potential candidate for lung cancer screening [9].

NLST and North American Practices

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 [10].

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 evidence [11]. Medicare coverage is provided for at-risk individuals. Unfortunately, however, uptake of the screening remains very low (only 1.9% of those eligible were screened in 2016) [12].

Researchers at the Veteran's Health Administration facilities conducted a study, which focused on real-life implications of LDCT screening. By using the data of the previously mentioned NLST, they assessed 90,000 and from those, screened over 2106 individuals in 8 facilities across the US. Factors leading towards the relatively small number of screenings performed include the lack of adequate smoking-history in the patient reports (PYs or time since quitting goes often unrecorded), and the low uptake of LDCT examinations (only 58% of the eligible individuals agreed to be screened). From the initially included 2106 individuals, 1186 had nodules that needed further tracking (31 proved to be lung cancer). Nevertheless, in 40.6% of the screened individuals other severe comorbidities (such as emphysema or coronary calcifications) were as well diagnosed. These data show how complex the real-world experience is, how much individual counselling is needed on the pre-screen level, and how much follow-up is needed after screening [13].

Studies now focus on further specifying the population that needs to be targeted. Although screening those who meet the United States Preventive Services Taskforce (USPSTF) criteria is already cost-effective, a large number of false positives could be eliminated by implementing additional screening criteria thus avoiding unnecessary CT examinations. When assessing the relative risk of different individuals, the PanCan study took into account the age, smoking duration, PYs, family history of lung cancer, educational level, body-mass index (BMI), chest X-rays in the past 3 years, and history of chronic

obstructive pulmonary disease (COPD). The ratio of early stage lung cancer found using these criteria was considerably higher (77%) than of those diagnosed in the NLST (54%). These criteria are now being further developed by using the data from the PLCO screening trial. These new additions suggest that heavy smokers between 65-80 years benefit most of lung cancer screening while never-smokers do not [14].

2.2. 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% [15,16].

Throughout Europe several different trials were conducted recently to assess the specific features of LDCT screening [17]. In Italy, MILD was initially launched to compare the

efficacy of annual and biennial LDCT screens, as the ethics committee did not approve the inclusion of an observational control arm. Therefore, statistical analyses were limited, and the MILD trial failed to show a benefit in mortality rate at 5 years. In contrast a significant reduction of lung cancer-related mortality rate could be detected at 10 years. The MILD trial has one arm with annual- and one with biannual screening rounds, and the efficacy of LDCT screening will be calculated in both study arms. In the bioMILD study (a different aspect of the MILD screening trial), 20 circulating diagnostic microRNA fragments are also taken into account. Accordingly, individuals in whom these microRNAs can not be detected from the blood stream are screened only in every 2 years, whereas patients with a high-risk miRNA profile undergo additional diagnostical testing [18].

In the United Kingdom, a population-based screening trial (UK Lung Cancer RCT Pilot Screening Trial, or UKLST) was also conducted recently. In this study, high-risk individuals were identified via personalized questionnaires. After the first screening round, the cost-effectiveness was calculated as Ł8466 per quality-adjusted life-year. The UKLST also provided valuable insights into the planning of a nationwide screening program. In their study, the researchers used the patient records of the National Health Service's Primary Care Trusts which enabled them to assess the attitude and willingness of different socioeconomic groups to participate on screening. The study also showed that significant efforts have to be done in order to reach the so-called "hard-to-reach" individuals. One potential solution to reach these individuals is to use mobile screening units which alleviate busy CT services from the screening workload while targeting difficult areas [19,20]

In 2015, the European Respiratory Society and the European Society of Radiologists published a joint ERS/ESR statement [17]. This was followed by the European position statement on lung cancer screening in 2017 [21]. 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. National quality assurance is a must to ensure that technical standards are met and that a

clear pathway is drawn for screen-detected nodules. Nodule growth should be measured by semiautomatic volume measurements. For now, only annual screening rounds are evidence-based, but in the future more personalized approaches with longer time gaps between screening rounds should be implemented for certain individuals. Notably, however, the most important statement from the paper is that "The EU position statement expert group recommends that the planning for low-dose CT screening should be started throughout Europe because low-dose CT lung cancer screening has the potential to save lives."

2.3. Lung Cancer Screening Projects in Hungary

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 [22].

3. 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.

3.1. Study design

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.

3.2. Recruitment and participants

To ensure adequate follow-up, only centers with expertise in lung cancer imaging, respiratory medicine and pathology contributed to screening. In total, six thoracic centers participated. 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. The leading methods of recruitment included media or internet campaigns, websites, posters, newspaper advertisements and advertising leaflets. General practitioners, volunteer recruiters and other respected individuals of the community have also taken part in the recruitment processes. It is important to point out however, that no mass- or direct mailing approaches were used. 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 [23] 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.

3.3. Procedures

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. The diagnosis of COPD was confirmed and specific cut points for FER

(FEV1/FVC) and FEV1 were used to evaluate its severity [24]. At all screening sites the LDCTs were acquired using a Siemens SOMATOM Emotion 16-slice scanner (Munich, Germany) or, starting from 2015, a SOMATOM Definition Edge 128 scanner (Munich, Germany). 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, whereas the effective radiation dose below 4 mSv. Across screening sites data acquisition and screening conditions were standardized. Thin-section images were transmitted either to a local picture archiving and communication system server, or a dedicated local Syngo Siemens (Forchheim, Germany) workstation for evaluation. A 2-megapixel greyscale monitor (EIZO RadiForce GX240, Hakusan, Ishikawa, Japan) at lung windows (width 350 HU, level 50 HU) and mediastinal windows (width 1700 HU, level -600 HU) were used for evaluation. 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 by the software's built-in matching algorithm (Siemens SyngoVia MM Oncology Lung Computer-Aided detection [CAD]) and also visually checked by the radiologists. The aforementioned software also calculated the VDT, defined as the number of days in which the nodule doubles in volume [23]. Of note, VDT is a theoretical number, which was devised to better estimate the growth of small nodules. It requires semiautomatic or fully automatic software measurements of the nodule's volume in at least two time points. The rationale behind this measurement is that the previously used diameter measurements in the axial

plane in nodules around one centimeter do not increase as rapidly as the three-dimensional measurements. The 2D measurements also vary widely from radiologist to radiologist, as this relies on a subjective manual technique. 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.

3.4. Follow-up and nodule-management protocol

The detailed nodule management protocol used by the HUNCHEST program is summarized in. (Figure 1) Concisely, a screening could be negative, indeterminate, or positive depending on the volume, growth and VDT. Participants with no detectable nodules (or well described benign lesions) were invited to participate in the next screening round 12 months after the baseline LDCT, whereas short-term follow-up LDCT was scheduled for those with indeterminate screening outcomes within the next 3-6 months. On the other hand, participants with positive screening results were referred to an expert pulmonologist, who then decided about further diagnostic and/or therapeutic procedures in accordance with the current National Comprehensive Cancer Network (NCCN) guidelines [25, 26]. Further diagnostic procedures included (but were not limited to) full-dose contrast enhanced chest or full staging (including brain, chest-abdomen-pelvis) CT, PET-CT, bronchoscopy, transthoracic needle biopsy (TNB) or video-assisted thoracoscopic surgery (VATS). If a patient was diagnosed with lung cancer, stage, pathological features and treatment offered were as well recorded.

3.5. Statistical analysis

The SPSS Statistics 26.0 package (SPSS Inc, Chicago, IL, USA) and GraphPad Prism Version 8 were used to perform all statistical analyses. Data distribution was verified by the Kolmogorov-Smirnov normality test. The number of true-positive cases divided by the sum of true-positive and false-positive cases determined the positive predictive value (PPV). Differences in distributions of baseline characteristics of participants in different smoking habit/comorbidity subgroups were statistically analyzed by $\chi 2$ test or Fisher's

exact test. The Mann-Whitney U test and Student's t-test were performed to analyse the continuous variables, and these are presented as means and standard deviations (normal distribution) or as medians and interquartile ranges (skewed distribution). Differences between groups were considered to be statistically significant at a P value of <0.05.

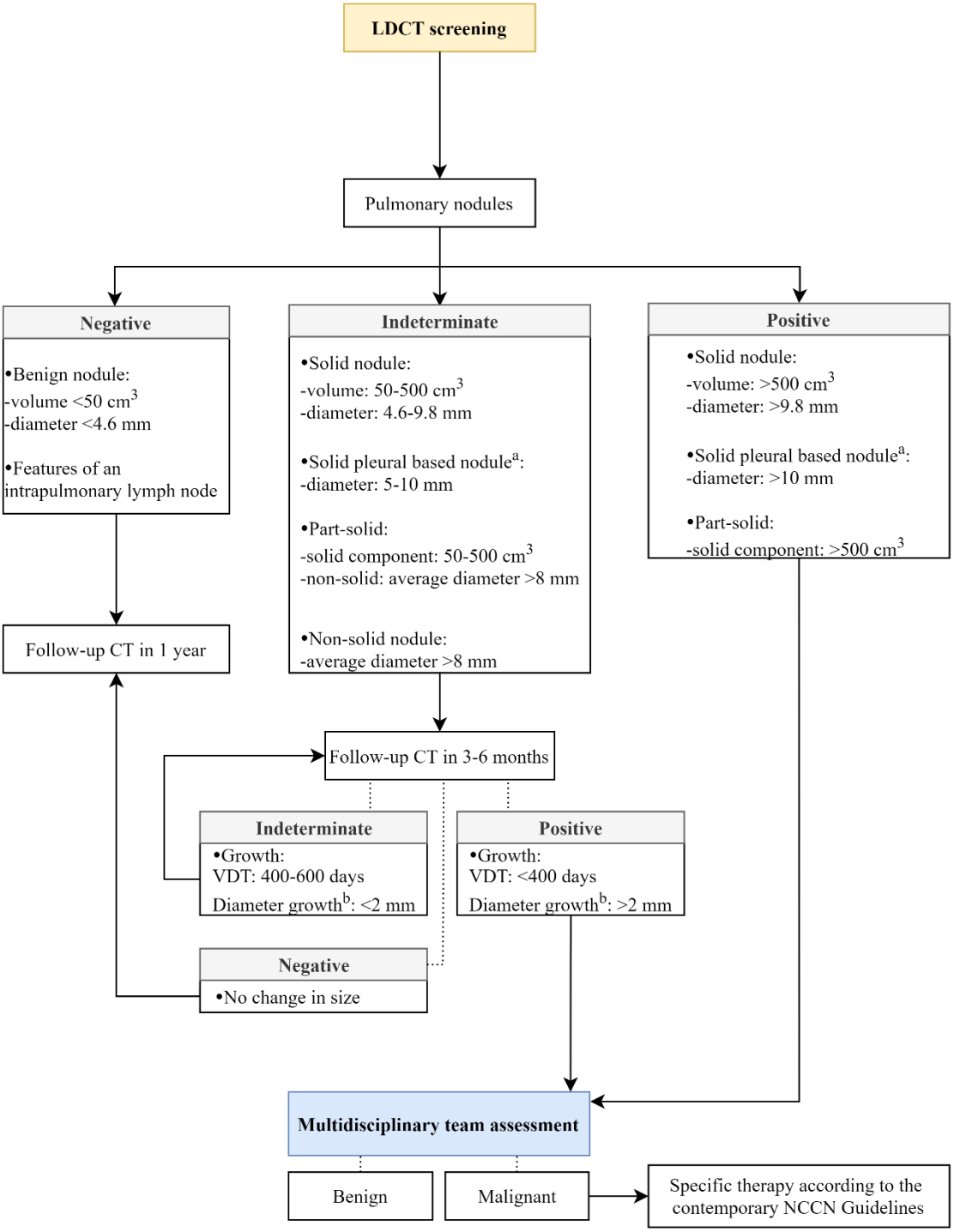

Figure 1 The HUNCHEST nodule care pathway management protocol[58]

4. Results

4.1. Characteristics and baseline screening results of enrolled participants

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; Table 1). 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 (Table 2). The average age of participants with positive or indeterminate screening results was significantly higher compared to those with negative results ($p<0.001$; Table 2).The incidence of both positive and indeterminate results was in fact the highest in participants aged between 61 and 65 years, whereas the lowest in individuals aged <55 years (Figure 2). The frequency of positive and indeterminate LDCT results was also significantly higher in current smokers (vs. non-smokers or former smokers; $p<0.0001$) and in individuals with COPD (vs. those without COPD, $p<0.001$) (Table 2 and Figure 2). It is important to point out however, that no significant differences were detected with regard to sex (p=0.446, Table 2) concerning the incidence of LDCT outcomes. Following the baseline scan patients with positive outcomes were referred immediately to the multidisciplinary team (MDT) assessment.

Table 1 Clinicopathological characteristics of the HUNCHEST study participants[58]

	Overall	**Non-smokers or former smokers**	**Current smoker**	**p value[a]**
Age (years)	63.216 95% CI [62.9, 63.6]	64.489 95% CI [63.9, 65]	62.13. 95% CI [61.7, 62.6]	<0.001[b]
Gender				
Male	819 (43.3%)	363 (41.7%)	456 (44.7%)	0.192[c]
Female	1071 (56.7%)	507 (58.3%)	564 (55.3%)	
Comorbidity (COPD)				
Yes	351 (18.6%)	103 (11.8%)	248 (24.3%)	<0.001[c]
No	1539 (81.4%)	767 (88.2%)	772 (75.7%)	

[a]p values refer to differences between non-smokers or former smokers and current smokers, [b]Student's t-test; [c]$\chi 2$ test; COPD, chronic obstructive pulmonary disease.

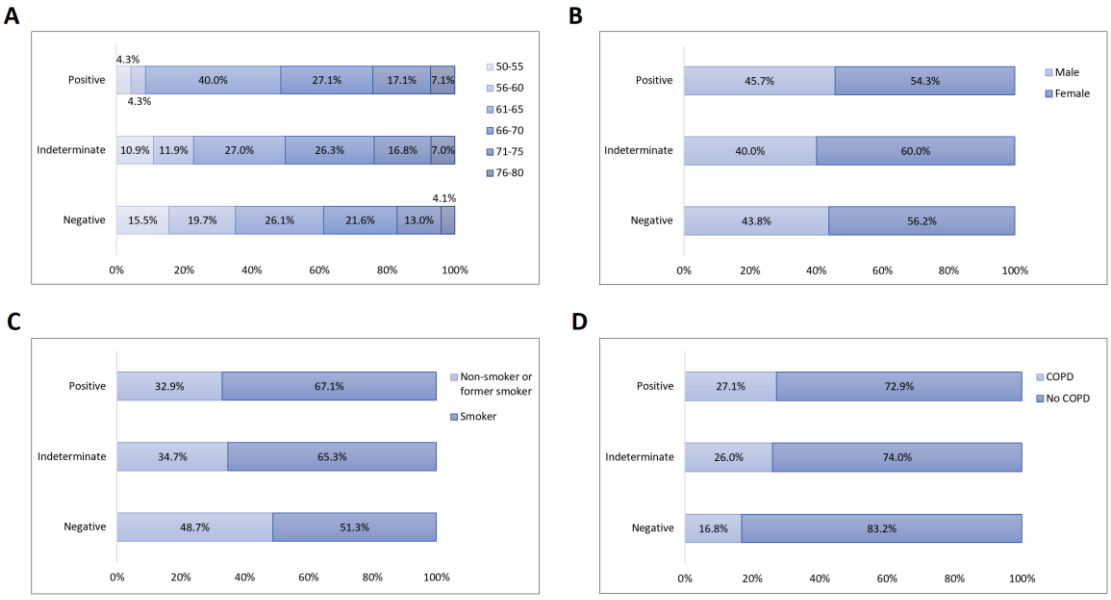

Figure 2 Percentage of individuals with negative, indeterminate and positive baseline screening results according to age (A), gender (B), smoking habit (C) and comorbidity(D)[58]

Table 2 Basic characteristics of the study participants according to baseline LDT screening results[58]

	Negative	Indeterminate	Positive	p value[a]
All participants	1535 (81.2%)	285 (15.1%)	70 (3.7%)	
Age (years)				
<65	940 (84.2%)	142 (12.7%)	34 (3.0%)	<0.001[b]
≥65	595 (76.9%)	143 (18.5%)	36 (4.7%)	
Gender				
Male	673 (82.2%)	114 (13.9%)	32 (3.9%)	0.446[b]
Female	862 (80.5%)	171 (16.0%)	38 (3.5%)	
Smoking history				
Non-smokers or former smokers	748 (86.0%)	99 (11.4%)	23 (2.6%)	<0.0001[b]
Current smokers	787 (77.2%)	186 (18.2%)	47 (4.6%)	
Comorbidity (COPD)				
Yes	258 (73.5%)	74 (21.1%)	19 (5.4%)	<0.001[b]
No	1277 (83.0%)	211 (13.7%)	51 (3.3%)	

[a] p values refer to differences between the screening result subgroups, [b]χ^2 test; COPD, chronic obstructive pulmonary disease.

4.2. LDCT results of follow-up screening rounds

In Figure 3 the participation flowchart of the HUNCHEST lung cancer screening trial is presented. In the second screening round, 21 individuals had positive outcomes (prevalence: 2.7%) irrespective of the initial screening results (i.e., negative or indeterminate), whereas negative and indeterminate results were seen in 653 and 122 cases, respectively. Unfortunately, 935 individuals from the initially test-negative subgroup and 89 participants from the indeterminate subgroup were not included in the second-round screening. The most common reasons for dropout were that the participant withdrew following consent or a scan was felt to be inappropriate as a result of a change in his/her health. Some patients were lost in the follow-up pipeline, despite continuous calls by the study nurse. At the third follow-up, 8 patients required further workup by the pulmonologists because their LDCT scans were test-positive leading to 99 screening-detected positive cases in total. Additionally, 115 negative and 38 indeterminate cases were also noted in the so-far last screening round. The remaining 153 patients are still under observation as of date.

4.3. Suspicious findings and lung cancer incidence during the active screening period

Table 3 shows the histologic features of positive solid nodules detected during first, second or third screening rounds. 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 (Figure 3). 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 (Table 3). Reflecting the early stage, 25 of 29 subjects had lung resection surgery (with or without adjuvant chemo- and/or radiotherapy) as their primary treatment.

Table 3 Histologic features of positive nodules detected during first, second and third screening rounds[58]

	Benign	Malignant	N/A[a]	p value[b]	Histological type[c]			
					ADC	SCC	SCLC	Other[d]
All participants	63 (63.6%)	29 (29.3%)	7 (7.1%)		18 (62.1%)	7 (24.1%)	2 (6.9%)	2 (6.9%)
Age (years)								
<65	31 (67.4%)	12 (26.1%)	3 (6.5%)	0.484[c]	8 (66.7%)	3 (25.0%)	1 (8.3%)	0 (0.0%)
≥65	32 (60.4%)	17 (32.1%)	4 (7.5%)		10 (58.8%)	4 (23.5%)	1 (5.9%)	2 (11.8%)
Gender								
Male	29 (63.0%)	13 (28.3%)	4 (8.7%)	0.914[c]	7 (53.8%)	5 (38.5%)	1 (7.7%)	0 (0.0%)
Female	34 (64.2%)	16 (30.2%)	3 (5.7%)		11 (68.8%)	2 (12.5%)	1 (6.3%)	2 (12.5%)
Smoking history								
Non-smokers or former smokers	22 (68.8%)	8 (25.0%)	2 (6.3%)	0.485[c]	7 (87.5%)	1 (12.5%)	0 (0.0%)	0 (0.0%)
Current smokers	41 (61.2%)	21 (31.3%)	5 (7.5%)		11 (52.4%)	6 (28.6%)	2 (9.5%)	2 (9.5%)
Co-morbidity (COPD)								
Yes	24 (75.0%)	6 (18.8%)	2 (6.3%)	0.098[c]	4 (66.7%)	2 (33.3%)	0 (0.0%)	0 (0.0%)
No	39 (58.2%)	23 (34.3%)	5 (7.5%)		14 (60.9%)	5 (21.7%)	2 (8.7%)	2 (8.7)

[a]Histological diagnosis could not be established due to patient withdrawal, [b]p-values refer to differences between the *Benign* and *Malignant* subgroups (all patients), [c]in case of malignant tumors, [d]other primary malignancies such as large cell neuroendocrine carcinoma or carcinoid tumors, [c]χ^2 test; ADC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; COPD, chronic obstructive pulmonary disease; N/A, not available.

Of note, the remaining 4 patients were not eligible for surgical resection due to advanced-stage lung cancer and received standard of care chemotherapy solely. There was no operative mortality or any death from surgical resection within 90 days. With regard to benign nodules, the most frequently diagnosed alterations were inflammatory nodules, intrapulmonary lymph nodes or benign hamartomas.

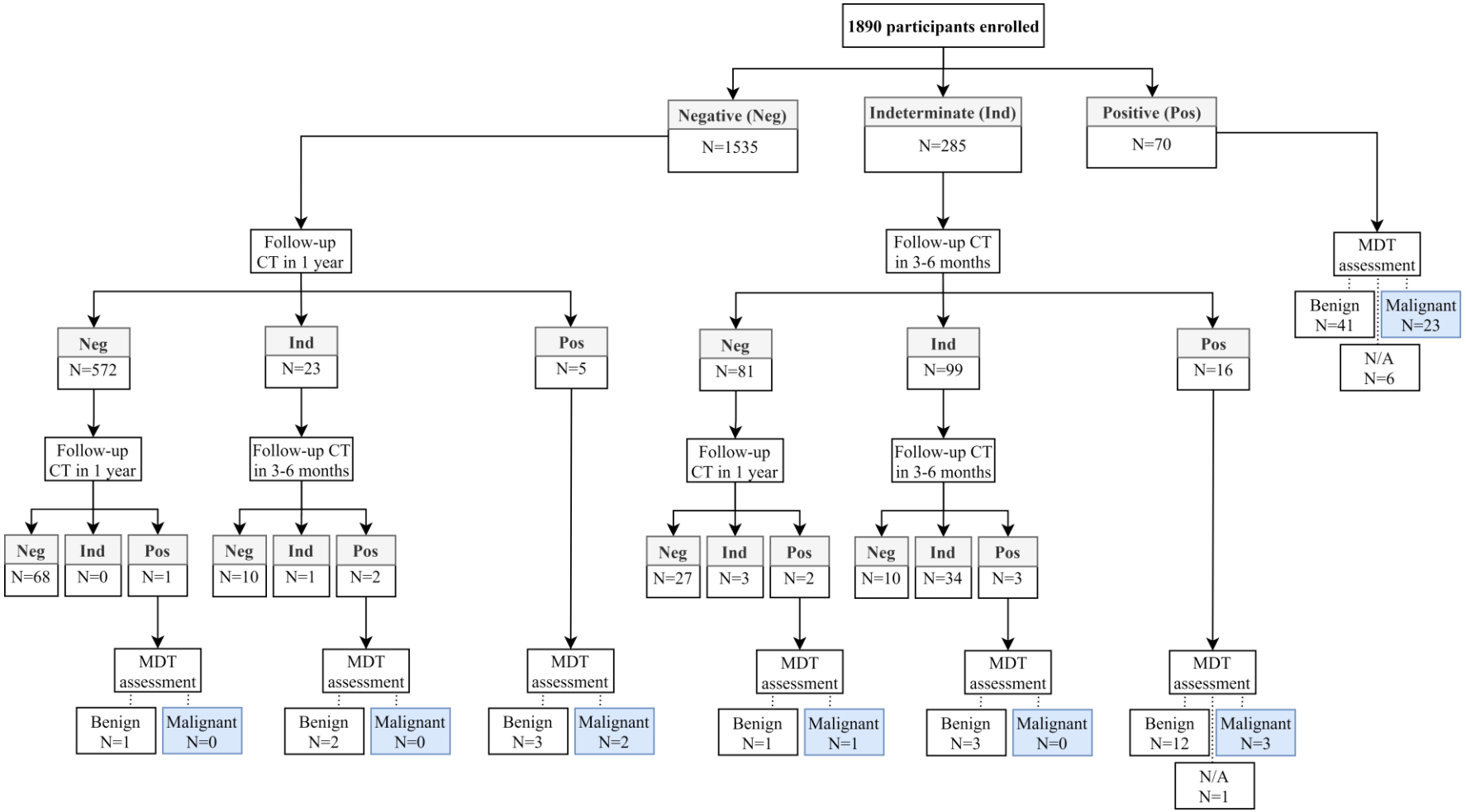

Figure 3 The participation flowchart of the HUNCHEST screening trial [58]

5. Discussion

Lung cancer is the most commonly diagnosed tumoral entity and the leading cause of cancer-related deaths both in Hungary and worldwide [27, 28]. In Hungary, 6,996 to 7,158 new lung cancer cases were recorded annually between 2011 and 2016, and 6,045 to 6,465 deaths occurred each year in that time period [27, 28]. Importantly, only approximately a quarter of these patients were diagnosed with early-stage lung cancer when the survival is more promising than in advanced-stage disease. This is a clear rationale for seriously considering a national early detection screening program. In the HUNCHEST pilot program, we aimed to assess the lung cancer probability of solitary pulmonary nodules, provide information about stage and cancer histology, and additionally, enhance the detection rate of early-stage lung cancer.

In contrast to other population-based screening trials (such as the aforementioned NELSON [29], the Italian LUSI [30] and several Chinese [31] lung cancer screening trials), in our study, participants were enrolled regardless of risk factors (i.e., smoking habits and comorbidities). In addition, they were enrolled on a voluntary basis without the application of active recruitment strategies. Therefore, when comparing the results of our study with the findings of others caution is needed. In the present study, the prevalence of positive results (3.7% at baseline and 5.2% overall) was considerably lower than in the NLST (24%)[4], but slightly higher compared to the NELSON trial (2.1%) [29]. The different selection criteria and nodule-management protocols of the NLST are the main reason for the discrepancy. Since the widespread use of multiline detectors, radiologists are often faced with a large number of insignificant benign nodules among a small proportion of early stage malignancies. Adequate nodule-management systems are therefore needed in order to reduce the number of false-positive screening results. When the NLST trial was designed, the contemporary follow-up protocol was much stricter than nowadays, making it necessary to classify every nodule above 4 mm of diameter as a positive screen. The NELSON trial used volume-based nodule-management protocols, whereas in the NLST the preferred method was a diameter-based nodule-management scheme. Importantly, in accordance with the NELSON trial, the researchers of the HUNCHEST project have decided to use volume-based measurement methods, and also to implement the indeterminate screening category [33]. Of note, the NELSON nodule

management system is reported to have one of the highest sensitivities and specificities among all management protocols designed for large-scale population-based screening programs [35, 29, 31, 34]. In the HUNCHEST study, the PPV of the positive screening tests was notably higher (31.6%) compared to the NLST (3.8%)[32], but lower than in the NELSON trial (43.5)[7]. Although smoking prevalence in Hungary decreased from the peak of 34% in 2003 to 28% in 2014, smoking and related illnesses still constitute a major health and economic burden [36]. It is not unexpected therefore, that according to the national register reports at least 2% of the country's adult population suffers from COPD with an even higher proportion being undiagnosed [37].

Since individuals were enrolled in the HUNCHEST pilot program regardless of their smoking behavior and COPD status, subgroup analyses concerning non-smoker participants could be also performed. Of note, the reason for recruiting non-smoker participants as well is that 10-25% of lung cancer patients are expected to be never-smokers [38]. In line with this, in the National Korányi Institute of Pulmonology (Budapest, Hungary) over 10% of all registered cancer patients were non-smokers in recent years (142/1394 in 2018 and 150/1452 in 2019).

A large proportion of lung cancers in non-smokers are ADCs (48.7-69.9%), while SCLS only occurs in 1.9-2.5% of cases. Squamous cell carcinomas are also rare among non-smokers. Defining precise risk groups in non-smokers is a difficult task since exposure to secondary smoke, radon and asbestos, cooking smoke (especially in Asia), viral infections, hormonal changes and pulmonary diseases all contribute to lung cancer. In younger patients, genetic factors also play a key a role in the development of this devastating disease, especially when there is a familial disposition. Among ADCs the EGFR oncogenic driver mutation is fairly higher in non-smoker patients compared to those with smoking history (47.9-74.7% vs. 11.3-18.9%, respectively). Of note, this discrepancy concerning the occurrence of EGFR mutations is even higher in Eastern Asia.

In our study, subgroup analyses were performed taking into account the presence or absence of COPD and smoking status. These analyses revealed that the incidences of both indeterminate and positive LDCT findings were significantly higher in smokers (vs. former-, or non-smokers) and in COPD patients (vs. participants without COPD). Given the high prevalence of benign inflammatory nodules in COPD patients these results were not unexpected, yet might serve as a basis for eligibility criteria in future trials. Notably,

to the best of our knowledge, the HUNCHEST screening trial is among the first studies together with the UK-based UKLS trial[9][39] to evaluate the efficacy of LDCT screening in Caucasian never-smoker participants with regard to COPD.

In the first screening round, 1.2% of the participants had a malignant lesion, whereas after three screening rounds, 29 (1.5%) individuals were diagnosed with malignant lung tumors. The previously published trials reported a range between 0.8% and 2.2%, and notably, the incidence of lung cancer in our study also lies within this spectrum [29, 32, 40-42]. Of note, no significant association was found between smoking habits and COPD, and tumoral entity (i.e., malignant or benign). Importantly, however, eight diagnosed lung cancers were found in patients who never smoked (or are former smokers who quit over 15 years ago) and had no history of COPD. Although, in contrast to others, in our study non-smoker patients were also included, the detection rates of lung cancer are surprisingly close to those from other trials. These findings suggest that screening of non-high-risk individuals might be also needed in the Hungarian population. In our study we also analysed the distribution pattern of the pathological stage of malignancies and found that the proportion of early-stage lung cancers was 86.2% (Figure 4). This is also in line with the findings of previously published international screening trials [29, 30]. Histologically, in line with the findings of the NELSON trial (60.6%) [29] and others [40,43], most lung cancers detected were adenocarcinomas (62.1%). VDT was reported to be a plausible indicator of cancer aggressivity and is a useful tool in the classification of screen-detected nodules [44]. In our study measurement of VDT contributed to the detection of malignancy in 6 of 29 (20.6%) lung cancers. LDCTs contain information not solely about lung nodules, but also of other abnormalities. In the HUNCHEST screening program, a variety of other important benign conditions were also diagnosed including severe emphysema, bronchiectasis, hamartomas and also extrathoracical entities such as kidney cysts. Although it is not possible to measure the effect of the early diagnosis of these lesions in this study, it is important to point out that the majority of these benign diagnoses were previously unknown by the participants and their physicians, and the detection of these conditions may further benefit the subjects.

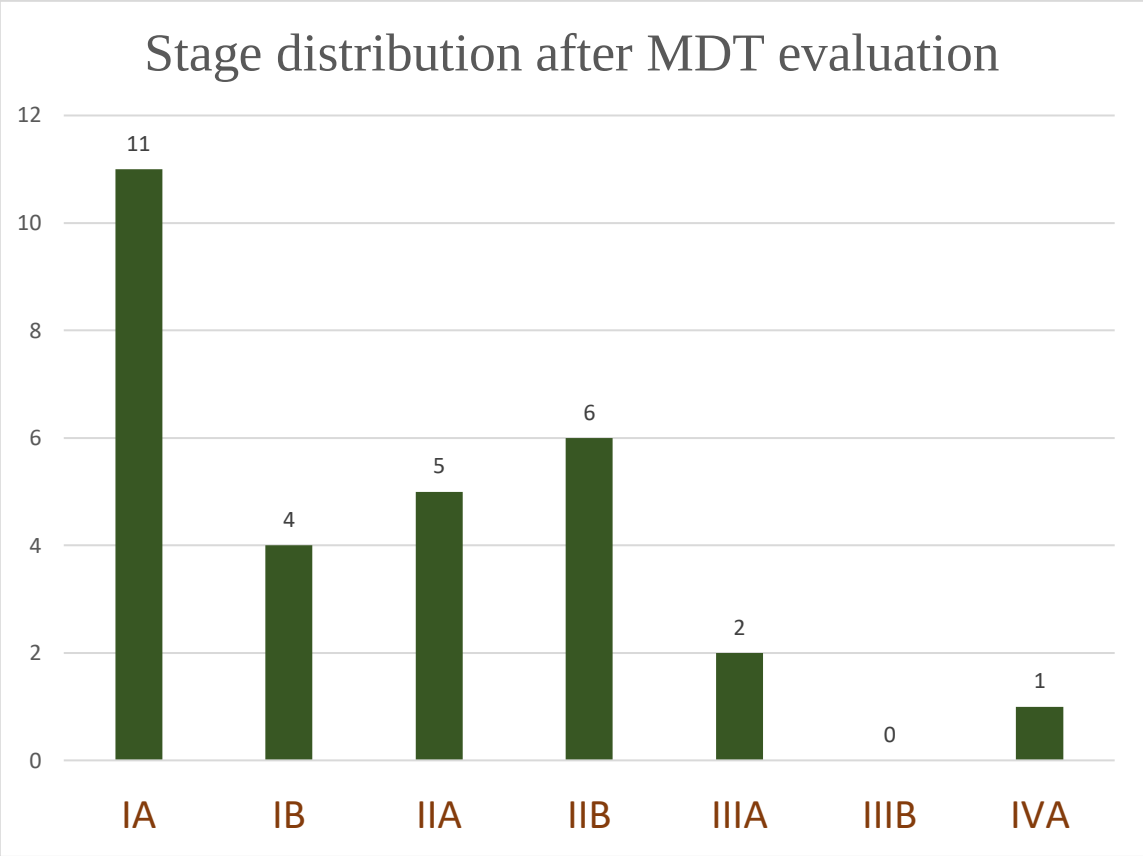

Figure 4 Stage distribution after MDT evaluation

The limitations of the HUNCHEST screening program require some discussion. Our study primarily aimed to determine the occurrence of positive solid nodules by LDCT and participants with no or negative findings were not closely monitored as part of the work-up. Therefore, the main limitation of the HUNCHEST pilot program is the lack of appropriate overall participant follow-up data and the absence of a clinically relevant control group. Specificity, sensitivity and negative predictive value could not be assessed due to the lack of the close monitoring in the initially test-negative subgroup. Despite the fact that no active recruitment strategies were followed, the number of participants who underwent baseline screening was relatively high. The compliance was poor however in the second and third screening rounds and the majority of the initially included individuals did not take part in the follow-up examinations. The lack of detailed information on the smoking habits in smoker participants constitutes another limitation. When stratifying participants into different risk groups not only the PYs but also the smoking duration, smoking intensity and cigarette type should be taken into account [45]. Second-hand

smoking was not considered either, despite the fact that it also plays an important role in lung cancer development [46]. Furthermore, although alluded to in the questionnaires, occupational hazards such as asbestos [47, 48], dust [49] and radiation [50] (which are are also associated with lung malignancies) were not statistically relevant. And finally, no specific approaches were applied in case of new solid nodules which were detected during follow-up scans. According to more recent studies, since these new nodules have a higher probability of lung cancer than baseline nodules, they should be followed up more aggressively by using lower volume cut-off values [34]. To overcome the aforementioned study limitations and further expand the nationwide lung cancer screening program in Hungary, in 2019 an implementation study, the HUNCHEST-2 was initiated. HUNCHEST-2 aims to examine the efficacy of LDCT screening in 6000 current- or former smoker participants and to optimize patient pathways following a positive screen.

The HUNCHEST pilot program is the first nationwide LDCT screening trial in Hungary. Our trial appears consistent to that of comparable studies in terms of key characteristics including positivity rate and PPV of the positive screening tests. Most importantly, the detection rate of lung cancer also lies within the range of the previous trials. Altogether, our results suggest that volume-based LDCT screening may facilitate minimal invasive treatment and can be performed with a relatively low rate of false-positive screen results. Nevertheless, further unresolved questions remain and more research with long-term follow-up is needed. The ongoing HUNCHEST-2 trial might provide a rich resource to address these remaining questions in order to define ideal screening guidelines for lung cancer in Hungary. How can we further optimize screening? The answers are multifold. With technological advances, lung nodules can be detected with lower and lower doses, and even today, scanners that can perform a chest scan with 0.1 mSV are commercially available. These new technological advances reduce considerably the risks arising from radiation even in a low-risk population. However, technological advances also increased the number of CT and MRI examinations performed, and the number of radiologists did not keep up with the demand. Therefore, computer-assisted technologies (from the simple computer-aided diagnostics ((CAD)) to the more advanced deep learning algorithms) will play an increasing role in the future.

In 2012, the NELSON researchers have randomly chosen 400 screening scans and had a

CAD system run through them. The sensitivity of CAD was 96.7% as opposed to the double human readings of 78.1 %. It is important to note, that there were only five semisolid nodules in the cohort, and two of them went undetected by CAD. Meanwhile, if the system was calibrated not to detect nodules below 6 mm, the false positivity rate dropped to 1.9%, which was considered acceptable [51]. CAD is now a part of the routine screening, and is essential in correct volumetry – either in its semiautomatic or automatic form [52].

The so-called radiomics uses all physical parameters obtained during a CT examination in mathematical algorithms in order to assess and "learn" the histological features of a nodule. Within research facilities, progress is being made, but real-life reproducibility is still weak. Probably the most awaited methods are the so-called deep-learning algorithms that are based upon hundreds and thousands of nodules. In the near future, these computer algorithms might be able to read a large number of cases rapidly, and if both false negativity and false positivity rates are on an acceptable level, they might replace human reading within special screening environments [53, 54]. As opposed to diagnostic radiology, which is a consultative process, screening radiology consists of a large number of scans without a clinical question. In the future, we have to debate whether it is ethical and legally acceptable if these CT scans are only machine-read since this might result in certain pathologies (which were not aimed to be diagnosed by the algorithm) going undetected. If yes, this will certainly diminish the screening costs, and thus the economic parameters of screening trials concerning non-smokers might also improve.

Finally yet importantly, the identification of different risk groups among smokers is also necessary. The identification of easily accessible biomarkers would enable us to select for screening only those who have a higher than average risk for the disease. Blood, urine or exhaled breath samples could all be tested. Autoantibodies, complement fragments, microRNAs, circulating tumor DNAs might all constitute possible biomarkers [55]. Unfortunately, however, to date, no tests are available in such a large quantity that would enable the screening of a whole population.

The combination of these three methods (lowered radiation dose, partly computerized detection of nodules, and the use of possible biomarkers) might represent a step forward in the lung cancer screening of the non-smoking population.

The long-term objective of our pilot project is the implementation of a LDCT lung cancer

early detection programme within the framework of national health. The term “early detection” is preferred for LDCT screening, as the test does not screen for precancerous lesions, but aims to find established (but still asymptomatic) malignancies. The first step towards implementing a nationwide screening program is to clearly define the target group which needs to be screened. This is followed by standardizing the techniques used for screening, and by implementing a clear management and follow-up protocol. Importantly, in the HUNCHEST pilot program we have used screening techniques that can be easily adapted by any radiological department with an adequate CT scanner (at least 16 slices, preferably >64). However, it also became evident that the lack of standardized softwares makes the data comparison difficult, and the VDTs calculated could be more easily compared if these softwares would be standardized. The management of the nodules as well as the follow-ups were conducted in the same way at every centre. HUNCHEST is also the first Hungarian LDCT screening program which used a web-based structured reporting platform (https://hunchest.koranyi.hu/). Based upon our results, we can conclude that screening the male and female heavy smokers between 50-74 years of age is cost-effective, whereas between ages of 55-74 is cost saving. These conclusions are all positively reinforcing the belief that a LDCT early detection program would be feasible in Hungary [56, 57].

By the end of 2019, the preparation for the so-called implementation programs was underway keeping up with the 2017 European position paper. And how does an implementation trial differ from a pilot program? The first major difference is that the project no longer focuses on its own screening results solely, but the efficacy of LDCT early detection is already established in the international literature (including the results of the HUNCHEST pilot study). The main aim is to involve several more screening sites that work independently and measure different cornerstone data. One of the most important aspects is to reduce the time interval between the positive screening results and MDT assessment and ultimately diagnosis (via different examination protocols such as bronchoscopy, biopsy, surgery or PET/CT etc.). The HUNCHEST pilot project offered valuable insights to overcome these aforementioned issues, and to implement a centralized data archivation and CAD system. Importantly, these systems allow a standardized data work-up and promote diagnosis, since by using CAD one radiologist is enough for diagnosis as opposed to the original HUNCHEST pilot study in which two

independent radiologists had to be recruited. In this second study, besides using the already well-estabilished forms from the original study, a complementary and well-structured reporting form for the follow-up procedures was also introduced. The implementation of this large-scale project was somewhat hindered by the COVID-19 pandemic, but hopefully, the preliminary results will be presented soon.

6. 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.

7. Summary

Lung cancer is the leading cause of malignancy-related deaths worldwide. For decades, screening programs for this devastating disease proved to be unsuccessful. Recently, however, the implementation of LDCT into the nationwide screening programs has led to the first clinically relevant progress in the field of lung cancer screening. The most important screening trials so far were the U.S.-based NLST and the Dutch-Belgian NELSON trial. While the researchers from the NLST reported a reduction of lung cancer-specific mortality of 20% in a 10-year follow-up, one of the main findings of the NELSON trial was that lung cancer mortality was considerably lower among individuals who underwent LDCT screening than among those who underwent no screening. Accordingly, both studies support the implementation of nationwide screening programs. Although an initial opportunistic LDCT screening program was already performed in Hungary with a limited number of participants, the HUNCHEST pilot project is the first Hungarian nationwide screening program which was implemented in multiple thoracic oncology centers and used a concise protocol of well-defined inclusion and exclusion criteria, nodule management assays (including VDT calculations), double-blinded reading processes, and nodule follow-up workflows. Together with the web-based structured reporting platform, these aforementioned protocols proved to be effective and easy-to-implement in all participating centers. In our pilot screening program, a total of 1890 participants aged between 50 and 79 years were assigned to undergo LDCT screening, with intervals of 1 year between procedures. At baseline, the percentage of negative, indeterminate and positive tests was 81.2%, 15.1% and 3.7%, respectively. With regard to lung cancer probability, 1.2% of the participants had a malignant lesion in the first screening round, whereas, altogether 1.5% of the individuals were diagnosed with lung cancer. The overall PPV of the positive tests was 31.6%. In terms of key characteristics, the results of the HUNCHEST screening program appear consistent to that of comparable studies, and the detection rate of lung cancer also lies within the range of the previous trials. Altogether, these results provide a clear rationale for considering additional national screening programs.

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