SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The Status and New Possibilities of Lung Cancer Screening in Hungary with the Application of Low-Dose CT Imaging

by Marianna Moizs MD

Supervisor: Imre Repa MD, PhD

UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF HEALTH SCIENCES

DEBRECEN, 2015

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Supervisor: Imre Repa MD, PhD

Doctoral School of Health Sciences, University of Debrecen

Head of the **Examination Committee**:

Róza Ádány, MD, PhD, DSc

Members of the Examination Committee:

László Nagymajtényi, MD, PhD, DSc
Ervin Berényi, MD, PhD

The Examination takes place at Department of Preventive Medicine, Faculty of Public Health, University of Debrecen,
9th December, 2015, 11 am

Head of the **Defense Committee**:

Róza Ádány, MD, PhD, DSc

Reviewers:

Tibor Baranyai, MD, PhD
Karolina Kósa, MD, PhD

Members of the Defense Committee:

László Nagymajtényi, MD, PhD, DSc
Ervin Berényi, MD, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
9th December, 2015, 13 am

I. Precedents and Aims of the Dissertation

I/1. Precedents of the Dissertation

The incidence and mortality data of tumorous diseases are extremely high in Hungary, they are in a leading position in international comparison. From among them the malignant tumorous processes of the respiratory system (lungs, bronchi) emerge retroactively for several decades. Compared to international data the incidence of lung cancer is the highest in Hungary and concerning the mortality rate caused by lung cancer, Hungary is in the first place in the world. The malignant tumour of lungs takes the most human lives in Hungary independently of gender above the age of 40.
The importance of lung cancer is unquestionable from the point of view of public health.
At present smoking has been regarded as the main risk factor of lung cancer, besides this some other factors connected to age and other diseases and environmental and genetic factors are considered. Smoking is responsible for 85 % of death connected to lung cancer.

In more developed (with high national income) countries several measures (smoking has been cracked down and health consciousness has been improved) have been taken in the field of primary prevention as a consequence of which the deterioration of the trend has stopped and a slow improvement has started.
In Hungary the morbidity and mortality situation have not improved on the whole in spite of the late smoking prohibiton measures.
Besides the high rate of smoking it can be stated that health consciousness of the Hungarian population falls far behind with the one of the more developed countries. The third main reason is that the Hungarian public health and health care system do not have a comprehensive action plan for the prevention and then the treatment of lung cancer.

In the field of prevention – generally and concerning lung cancer as well – there is a coordination and communication disorder between the leaders, the suppliers, the target groups and the tasks, consequently the activists for the same goal work parallel and separately from each other including the supervision of the health care system, primary, outpatient and hospital care.

In Hungary the participation in organized screening tests falls far behind the measure required by WHO. There is no organized lung screening.
Its consequence is that the malignant diseases which can be screened, and in this way most of the lung cancer, are revealed in the clinical stage with advanced diseases, complaints, symptoms, when the possibility of effective treatment and survival is much less and the expenses of treatment are increasingly higher.

The lung screening system working effectively for decades, which had great professional traditions, fulfilled its original mission. At present it works in a transitional condition, its task besides screening tbc is to screen lung cancer and COPD, but the fight against lung cancer as a priority has not been defined clearly. It has not been renewed in a comprehensive way, concerning either its structure or its methods.
With the ceasing of compulsory lung screening the country average of screening dropped to 25 %. The traditional chest X-ray screening based lung screening (even in a digitalized form) makes it possible to detect the early, stage I tumour only in the case of 25-30 % of tested patients. The lung cancer do not have striking clinical symptoms in an early stage and belongs to the little curable tumorous illnesses at an advanced stage.
The long term survival of patients is very low (the average 5 year survival is 10-15 %) in spite of the fact that surgery, radio- and chemotherapy modalities have developed. During the detection of lung cancer patients at early stage radical resection could be performed at a larger scale, which improves the survival chances of patients considerably – with 40 % of survival on average and 60-70 % in the case of stage I patients.

In the past twenty years newer and newer guidelines concerning prevention and screening have appeared in the world, from among which CT based screening seems to be the most effective one for lung screening taking into consideration the data available.
CT based screening has brought definitive changes in survival and the decrease of mortality rate.
International multicentric studies have proved that low radiation dose CT (LDCT) examination is much more effective for lung cancer screening than chest radiography, because it is more sensitive to detect lung cancer at an early stage and it can record the expansion tendencies of the tumour much more exactly.
LDCT screening is the only lung screening method for testing lung cancer recommended on evidence according to our present knowledge.

The several year long follow-up of LDCT screening trials have proved that 65-85 % of stage I lung cancer can be revealed and mortality caused by lung cancer can be reduced. Low-dose CT testing is relevant only in the case of groups with high risk of lung cancer.

It is evident as well that beside screening, smoking cessation is also part of lung cancer prevention programmes. With the integration of primary and secondary prevention, with the application of the principle of „screening is the teachable moment" the successfulness and effectiveness of the screening programme can be increased.

In my dissertation I would like to show the process that keeping the earlier system of lung screening for tbc and renewing, changing its target group and method what kind of steps must be made to transform it to the screening of the malignant processes of the lungs with low-dose CT on the basis of suitable scientific establishment.
The general aim of the dissertation is the decrease of the conspicuously high morbidity and mortality data connected to lung cancer in Hungary.
Its concrete aim is to work out a screening model which takes the Hungarian disease and appearance characteristics of lung cancer into consideration, defines a Hungarian risk group, can be fitted into Hungarian health care and social environment and serves the preparation for the LDCT lung screening evidencies in Hungary.

I/2. Aims

1. I have set the aim to examine the possible introduction of targeted, risk group lung cancer screening in Hungary.

2. I have set the aim to design the new technological model of Hungarian lung screening to detect lung cancer at an early stage with the application of 3 dimensional low-dose CT screening, which is considered to be the only effective secondary prevention technique at present.
   I have set the aim to define an LDCT based lung screening protocol.

3. I have set the aim to modernize the system of traditional lung screening.

4. I have set the aim to launch mobile LDCT based lung cancer screening in Hungary.

5. I have set the aim to do the first LDCT based lung cancer screening pilot research in Hungary.

6. I have set the aim to analyse the risk factors of lung cancer in the widest possible field and on the basis of this to define the target group taking part in the screening in the most optimum way.

7. I have set the aim to examine the increase of the voluntary participation of the population in lung cancer screening, then to establish an effective communication strategy.

8. I have set the aim to do preliminary estimation of expenses connected to LDCT based lung cancer screening.

II. Materials and Methods

The essence of LDCT technique is the reduction of radiation dose. Applying it together with computer assisted findings the exposure of the individual to ionizing radiation can be reduced besides maintaining suitable image quality.
The further advantage of LDCT technique is that it produces three-dimensional, volumetric testing compared to the two-dimensional image of chest X-ray tests. The size, types and relationship of nodules to the environment developed in the lungs can be judged much better and the growth and change of nodules in the same way during the follow-up examinations.

The LDCT examinations were done with 2x128-slice dual source CT equipment (Siemens Somatom Definition Flash, Siemens AG, syngo.via, oncology workflow, Erlangen, Germany) without intravenous contrast material.
The region examined spred during inhalation from the pulmonary apex to the bottom of pleural sinuses set individually on the basis of topogram. We defined the examination parameters on the basis of the industrial LDCT chest-CT program with 4D dose optimalization. 300-500 images were taken of one patient with 1 mm slice thickness.

The effective radiation dose was in the range of 0,8-1,5 mSv, significantly lower than the annual natural background radiation (2,5 mSv), so it did not mean significant exposure.
After the examinations the archivation happened in DICOM format (digital imaging and communications in medicine) on the server of the Institute of Diagnostics and Oncoradiology of Kaposvár University. For the evaluation of the images Siemens syngo.via oncology workflow program package and eRAD PAC (eRAD Greenville, USA) imaging program were used.
The changes of the nodules were analysed with the comparison of diameters in the case of subpleural localization, in the case of intraparenchimal nodules – as the possibility of growth emerged on the basis of the measuring of the diameter and if it was technically applicable – with volumetric comparison.

During the baseline LDCT screening we determined the size, localization, density [solid (high density), non-solid (low density), mixed or partly solid], possible calcification, outlines (round/ovoid, lobulated, spicular), number (free from nodules, soliter, multiplex) of nodules demonstrable in the lungs.

If no nodule could be determined during the baseline examination, the next screening happened 1 year later.
If there was a lesion during the first screening, depending on the size, volume, density and other characteristics of the nodules detected, LDCT control screening was done 3 or 12 months later.

During the evaluation of cases suspicious of malignancy the most important parameters calculated were the average growth ratio and the volume doubling time.

The selection happened in the lung care centre of Moritz Kaposi General Hospital of Somogy County on the basis of age (above 40) among adults coming to lung screening voluntarily.

I separated 3 phases during the examinations:

In the first phase there was an examination with a questionnaire in the case of individuals who came to chest X-ray lung screening examination voluntarily and filled in the questionnaire compiled by me containing questions about life-style, screening examinations, lung screening. I looked for the answer in this phase of the research how often the individulas with different smoking habits took part in screening examinations and what motivated them to take part.
The questionnaires of the first phase were filled in by 1060 individuals.

In the second and third phase of the research in the case of the 173+185 (358) individuals I set conditions concerning their age and smoking habits. I defined if the results of the two groups were different on the basis of their age, smoking habits and LDCT findings.
In the second phase in the lung care centre we offered the LDCT examination to those individuals above 40 coming to the lung care centre voluntarily for lung screening who had a negative digital chest X-ray examination. After the CT examination the subjects filled in a questionnaire, which differed from the one used in the first phase in a way that it contained questions about willingness to pay.

In the third phase the LDCT examination was offered to those individuals coming to lung screening voluntarily, who were above 50. Parallel to the X-ray examination, 50 individuals agreed to take part in spirometric tests as well. After a negative chest X-ray examination we offered LDCT examination to those who smoke or used to smoke. After the CT examination the participants filled in the questionnaire applied in the 2nd phase.

On the basis of the above, the criteria for the inclusion for LDCT examination were the following:

- voluntary participation on CT examination
- smoker or earlier smoker individuals in the 3rd phase.

Exclusion criteria were viewpoints which did not meet the inclusion criteria and pregnancy.

III. Results and Discussion

The disease and death burdens of lung cancer in Hungary can only be reduced if the lung screening system – renewing its organization amd method, utilizing the possibilities of a network system, focusing on one target group – becomes suitable for detecting of lung tumour in an early stage.
The organization and the technical development of lung cancer screening and the introduction of an effective screening method, the definition and access to the risk group and the increase of their participation rate are urgent.

During the review of literature I have shown the epidemiological status connected to lung cancer in Hungary and imaging methods applied for lung screening. On the basis of international evidences the only effective screening method is the LDCT examination with the application of which lung tumour can be detected at an early operable stage, improving survival and decreasing mortality.

On the basis of the pilot examination the dissertation suggests a concrete model and protocol for the implementation of LDCT imaging as a risk group lung cancer screening method for the first time in Hungary as a mobile screening method as well.
Concerning the technology and the method, the results of the dissertation correspond to international literature, but the risk group, the organizational background and algorithm of the screening are different though, they are adapted to the Hungarian population and health care environment.

From a technological and methodological point of view the possible new model of lung cancer screening in Hungary is based on low-dose CT imaging. My working team have applied three-dimensional LDCT imaging and volumetry in lung screening in Hungary for the first time. I have introduced new evaluation parameters, the nodule volume and volume doubling time.

On the side of target group I have supported that lung screening must aim at lung cancer screening in Hungary and targeted, risk group lung cancer screening is suggested.

From a structural side the model can work with taking into consideration the good practice of the Hungarian lung screening system, with the utilization of the existing lung screening - lung care infrastructure, but with its renewal.
The lung care centers of county hospitals can be the centers for lung screening on a county health care level. The chest X-ray possibilities exist here and they cooperate with CT imaging diagnostic units. The concentration of high-technology diagnostic equipment in centers is necessary from the point of view of lung cancer screening, too. Complex oncological - lung cancer screening centers can be developed. Multidisciplinarity, onco-team like operation and the early access to definitive care of patients detected at screening are provided in this way. The renewed network is suitable for the organization of complex screening as well.

On the basis of the screening protocol worked out, the first step before the LDCT examination is risk assessment, then in the case of individuals belonging to the risk group as a preliminary screening we do a chest X-ray examination in accordance with the current laws so as to decrease radiation exposure and the expenses.
In a positive case (in the suspicion of lung cancer) we start check-up according to protocol. The LDCT examination is done in the case of negative chest screening findings.

The risks connected to screening can be decreased and the expected benefit will exceed those if we keep the following conditions: the screening should be done in centers of great practice with suitable protocol screening the ones of high risks.

An important element of the new model is that mobile screening stations complement the units of the screening system settled into the county centers. They must be integrated into the screening centers, but their scope of activity can exceed the county borders. The fixed and mobile LDCT lung cancer screening duality reflects the complex possibility of stable and mobile traditional lung screening. The target group of mobile screening are those persons, who do not access to the programmes in the screening centers because of settlement pattern, income, or lack of health consciousness and have high risk of lung cancer.
We started the complex screening with LDCT at the mobile screening stations for the first time in Hungary in 2014.

Preparing the introduction of LDCT lung cancer screening in Hungary in the first model research we found 1 lung cancer case out of 173 individuals over 40 without any complaints with CT during the control examination. Before that we detected 3 patients with lung cancer with chest X-ray.
In the second phase out of 185 individuals without any complaints belonging to the risk group on the basis of international recommendations (over 50, smoker or previously smoker), we diagnosed 3 lung cancers at the baseline LDCT examination and 1 lung cancer during control exams. We had detected 9 lung cancer patients with chest X-ray. Altogether the chest X-ray detected 12, then the LDCT 5 lung cancer patients.
The additional use of the LDCT was to detect 2 further tumorous cases.
In the two phases of the examination on the baseline CT images the lung cancer ratio was 0,0 % and 1,6 % in a state without any complaints, the same value in literature is between 0,4-2,7 %. On the follow-up CT images this ratio is 0,6 % and 0,5 %, which was between 0,07-1,1 % in international studies.

My results are the same as the data of professional literature, on the basis of which low-dose CT based lung cancer screening is suggested in the case of a well-defined risk group.
In Hungary the smokers and former smokers above 40 in the case of both sexes can be regarded as high risk groups of lung cancer.
Additional risk factors can be other tumorous diseases in case history and lung cancer in the family.

The stressed aim of lung cancer screening is that we can address the ones with high risk and provide 60-70 % screening rate for this group.
60-70% of a risk group as big as this (about 1,4 million Hungarian adult inhabitants) can be reached and screened with suitable organizational background and forced, aimed communication strategy, which – according to my results – can be founded on the media and health care professionals. The increase of the participation can be based on the health consciousness of the target group, their actual accessibility and individual responsibility, but it cannot be based on traditional, compulsory lung screening habits.

I stress that real and long-lasting result can be reached if secondary prevention is applied together with the primary one, LDCT based lung cancer screening can be combined with programmes which help giving up smoking and limiting smoking.

The pilot examination, which is the basis of the topic of the dissertation, aimed at the creation of a new lung cancer screening model. The number of cases did not make it possible to analyse the cost-effectiveness, which is not an aim of the dissertation. We can state that the treatment expenses of lung tumours at a late stage diagnosed with chest radiography are the highest compared to the whole diagnostics expenses and the treatment expenses of tumours diagnosed with LDCT.
The early diagnostics of lung cancer with LDCT results that the lesion can be treated in a curable way and it can be removed in toto with an operation. About half of the cases require adjuvant chemotherapy, radiotherapy more rarely and the expenses can be reduced in this way. From epidemiological and expense aspects the „shift" of tumour stages towards the early, operable lung cancer stage is a primary question.
Preliminary risk estimation, X-ray screening and decision optimalization (multidisciplinary team) help the cost-effectiveness of the screening, and the introduction of the complex screening of lung cancer, COPD and cardiovascular diseases can also help it.

It can be estimated on the basis of the macrolevel cost analysis that the present day late treatment of patients with lung cancer and the LDCT lung cancer screening of 67% of the total smoking population over 40 can mean the same cost for the financing.

Randomized, follow-up pilot studies and data collection and a health-economic model valid for Hungarian circumstances can answer further questions.
The following, multicentric research planned by my working team will possibly prove that early, effective, definitive oncological treatment can be applied with the participation in the new screening programme, with the early recognition of malignant lung cancers as a result of which the high mortality rate caused by lung cancer in Hungary on an international scale can be reduced.

IV. New Scientific Results

1. On the basis of the literature and my own results I have determined that the introduction of the targeted, risk group screening of lung cancer in Hungary is reasonable.
2. I have specified the LDCT based imaging model and protocol of lung cancer screening in Hungary.

   According to my knowledge, it is the first lung cancer screening model which applies LDCT imaging after chest X-ray examination. Its three main elements are the LDCT imaging after two preliminary tests, the risk estimation of lung cancer and a chest X-ray test with a baseline examination and comparative examinations based on protocol.

   I have defined the Hungarian criteria of detecting and follow-up with LDCT imaging concerning lung cancer.
3. I have defined the model of the structural reform of the Hungarian lung screening system.
4. I have done with my colleagues LDCT lung cancer screening put into a mobile screening station for the first time in Hungary, which is of great importance of reaching the target group.
5. I have done the first LDCT imaging based lung cancer screening pilot research, published the first model and results of LDCT imaging lung cancer screening in Hungary.
6. After the analysis of the risk factors, I have defined the target group of LDCT lung screening in Hungary.
7. Examining the participation willingness, habits of the Hungarian population in lung screening I have formulated proposals for the foundation of a targeted communication strategy, with the help of which the participation in the new LDCT lung cancer screening can be increased.
8. In connection with the first Hungarian clinical research of LDCT based lung cancer screening I have calculated the basic expenses, on the basis of which the detection with LDCT imaging and treatment of early lung cancer can be effective in Hungary.

Registry number: DEENK/155/2015.PL
Subject: Ph.D. List of Publications

Candidate: Marianna Moizs
Neptun ID: CVYD2M
Doctoral School: Doctoral School of Health Sciences
MTMT ID: 10026866

List of publications related to the dissertation

1. **Moizs, M.**, Bajzik, G., Lelovics, Z., Strausz, J., Rakvács, M., Zádori, P., Kovács, Á., Repa, I.: Characterization of Individuals Taking Part in Low Dose Computed Tomography (LDCT) Screening Program.
   Pathol. Oncol. Res. Epub ahead of print (2015)
   DOI: http://dx.doi.org/10.1007/s12253-015-9929-4
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2. **Moizs, M.**, Bajzik, G., Lelovics, Z., Rakvács, M., Strausz, J., Repa, I.: First result of differentiated communication-to smokers and non-smokers-in order to increase the voluntary participation rate in lung screening.
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List of other publications

3. **Moizs M.**, Bajzik G., Lelovics Z., Rakvács M., Strausz J., Repa I.: Alacsony dózisú CT-vel történő tüdőrákszűrés magyarországi bevezetésének első tapasztalatai.
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Total IF of journals (all publications): 4,176
Total IF of journals (publications related to the dissertation): 4,176

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

24 August, 2015

DEBRECENI EGYETEM KENÉZY ÉLETTUDOMÁNYI KÖNYVTÁRA EGYETEMI ÉS NEMZETI KÖNYVTÁR

Address: 1 Egyetem tér, Debrecen 4032, Hungary Postal address: Pf. 39. Debrecen 4010, Hungary
Tel.: +36 52 410 443 Fax: +36 52 512 900/63847 E-mail: publikaciok@lib.unideb.hu, ¤ Web: www.lib.unideb.hu