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Consensus statement on a screening programme for the detection of early lung cancer in Poland

Abstract

Introduction: Lung cancer is the most common cancer in Poland and worldwide, and the leading cause of cancer-related deaths. Compared to the present day, the annual number of new cases of lung cancer will have increased by approximately 50%, by 2030. The overall ratio of mortality to incidence totals 0.87 and is among the highest. The five-year survival rate in Poland has recently achieved 13.4%. In 2015, lung cancer screening using low-dose computed tomography (LDCT) was introduced to routine clinical practice in the United States following the publication of the largest randomised study, The National Lung Screening Trial. The implementation of screening programmes in Poland and the rest of Europe also seems unavoidable. Due to the differences, both in the socioeconomic considerations and healthcare funding, compared to that in the United States, the current approach comes down to the awaited results of the European randomised study, NELSON.

Material and methods: During the meeting of an expert panel at the “Torakoneptunalia 2016” conference in Jastarnia, Poland, a decision was made to summarise and publish the current data on LDCT lung cancer screening in the form of recommendations, or a position statement. The document was prepared by a team composed of a radiologist, thoracic surgeons, pulmonologists, clinical oncologists, epidemiologists, internists, health prevention specialists and pathologists. It reflects the current body of knowledge about lung cancer, its diagnosis and treatment, and provides recommendations on early detection of lung cancer using LDCT. The recommendations address the screening procedure, the requirements for the teams conducting the screening, and the requirements for radiologists, pathologists and surgeons involved in the diagnosis and treatment of patients.

Results: While awaiting the results of the NELSON study on lung cancer screening methodology, the multidisciplinary group of experts presents their position, laying grounds for the development of an action plan for early detection of lung cancer in the upcoming future in Poland.

Conclusions: Primary and secondary prophylaxis are the principal ways to reduce lung cancer mortality. While smoking cessation is a task of utmost importance, it must be accompanied by an effective screening programme if the outcome of the disease is to be improved.

Key words: lung cancer screening, early detection, secondary prophylaxis

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1. The epidemiology and treatment of lung cancer in the world, Europe and Poland

According to the World Health Organisation (WHO), lung cancer is the most common cancer in the world (about 1.8 million new cases annually, accounting for nearly 13% of all new cancer cases). Males account for 68% of all patients. Lung cancer kills an estimated 1.2 million people each year (17% of all cancer deaths) [1]. Approximately 85–90% of lung cancer deaths are closely associated with smoking, with non-smokers accounting for about 10–15% of all lung cancer patients [2]. Several studies investigating lung cancer unrelated to smoking have revealed exposure to certain carcinogenic factors (occupational exposure to risk factors, second-hand cigarette smoke, fume pollution at household, atmospheric smog). The molecular and genetic profile is of critical significance in this separate category of lung cancer [3].

The incidence of lung cancer shows a considerable regional variation. Due to the high mortality to incidence ratio totalling 0.87, mortality data can be regarded as an approximate measure of incidence. The highest mortality rates in men (about 50 per 100,000) are reported in the countries of Central and Eastern Europe (including Poland) and in Central and East Asia. The lowest mortality rates (about 2 per 100,000) are recorded in the countries of Central and West Africa. The pattern of prevalence of lung cancer in women is slightly different and also follows the distribution model of smoking, with the highest mortality rates being observed in North America (34 per 100,000) and Northern Europe (24 per 100,000), slightly lower rates being reported in the countries of Central Europe (including Poland) and Asia (below 20 per 100,000), and the lowest rates being found in

West Africa and the Middle East (about 1 per 100,000) [1]. In Europe, lung cancer was the most common cause of cancer mortality in men (254 thousand; 26%) and also accounted for 13% of cancer deaths in women (99 thousand) in 2012. Since the mid-1990s, a downward trend has been noted in the incidence of lung cancer in most European countries [4]. No such favourable trend is, however, observed in women [5]. In 2013, a 6% relative decrease compared to 2009 was noted in lung cancer mortality among men in the countries of the European Union, while mortality in women increased by 7% during that period, approaching the value in men [5–7].

In Poland, 14,600 and 7,000 new cases of lung cancer are diagnosed annually in men and in women, respectively (with age-standardised incidence rates of about 48 per 100,000 and 18 per 100,000, respectively), which accounts for 19% and 9% of all new cancer cases in men and in women, respectively [6]. Since 2007, lung cancer has continued to be the most common cause of cancer death not only in men (31% in 2013) but also in women (16% in 2013) [8].

The main cause of the lung cancer epidemic, both worldwide and in Poland, is tobacco smoke. This has been proven by many historical studies, both on the population [9] and biological [10] level. Association between tobacco smoking and risk of disease is a cause-effect and dose-response type of relation [11]. Reducing a population rate of tobacco smoking should be a priority for the healthcare system and a moral duty of every physician. Measurable benefits coming from such an approach were demonstrated in a theoretical model [12] and in empirical studies, also in Poland [12, 13]. The declining trend of lung cancer incidence and mortality in Polish men is the result of reduction in tobacco smoking. Unfortunately, this beneficial

phenomenon has not been observed among women. From the population viewpoint, the most effective action against lung cancer, is primary prevention leading to reduction of smoking prevalence.

Lung cancer is associated with a low survival rate, due to its long asymptomatic course that allows it to remain undetected until it is in an advanced stage. In the United States, the 5-year survival rate of lung cancer was reported at 17.4% [7]. The 5-year survival rates for lung cancer in the 67 countries participating in the CONCORD-2 study for the most recent follow-up period (diagnosed in the years 2005–2009) ranged from 2.2% in Libya to 16.5% in Switzerland, 18.7% in the United States and 30.1% in Japan. In Poland, survival has increased from 11.4% to 13.4% [14].

2. Detection of lung cancer

The clinical manifestations of lung cancer depend on its clinical stage, histological type, tumour location and the presence of distant metastases. In some patients, who are clinically asymptomatic, lung cancer is diagnosed incidentally on imaging during investigation of unrelated problems.

The most common symptoms of central and endobronchial tumours are cough and haemoptysis. Further growth of endobronchial tumours may lead to atelectasis, which is often accompanied by inflammatory or suppurative processes.

Peripheral tumours may also cause dyspnoea due to airway obstruction and symptoms associated with pleural infiltration such as pain, effusion or chest wall destruction. In patients with advanced disease, the most common manifestations include general symptoms (asthenia, weight loss, low-grade fever) and symptoms specific to the location of metastases (bone pain). In about 10–20% of the patients, the diagnosis of lung cancer is preceded by paraneoplastic syndromes (SIADH, carcinoid syndrome, Cushing's syndrome, Lambert-Eaton myasthenic syndrome, hypertrophic pulmonary osteoarthropathy, hypercalcaemia) [15].

The purpose of the diagnostic evaluation of lung cancer is to establish its histological type and stage. The principal elements of the diagnostic process in lung cancer are medical history, physical examination, imaging studies and invasive diagnostic procedures.

The main imaging modality used to diagnose lung cancer is computed tomography of the chest [16]. With the advent of low-dose computed tomography (LDCT), plain radiography is gradually losing its significance, although it is still the most commonly ordered investigation in clinical practice in Poland.

The purpose of non-invasive evaluation is to detect lung cancer and, if detected, to establish its TNM stage. PET-CT is the most valuable imaging modality in detecting metastases to mediastinal lymph nodes and to distant organs. Imaging is also useful in the monitoring of treatment efficacy.

The most common radiological manifestations of lung cancer include a coin lesion (solitary pulmonary nodule), hilar enlargement, atelectasis or emphysema and pleural effusion. PET-CT is currently used to detect remote metastases. Patients being considered for curative surgery or radiotherapy, require an assessment of pulmonary function (spirometry, diffusing capacity testing) and cardiovascular function (ECG, echocardiography).

The final diagnosis is established on the basis of histopathological or, less frequently, cytological examination. Tissue samples for examination are collected during bronchoscopy, EBUS/EUS, transthoracic biopsy of peripheral lesions, mediastinoscopy or thoracotomy. The resulting histopathological specimens are used to determine the histological type of the tumour (small cell lung carcinoma, adenocarcinoma, squamous cell carcinoma etc.) and to carry out molecular testing (activating mutations in the EGFR gene, ALK gene rearrangements etc.), which determines further targeted therapy. Cytology is of limited diagnostic significance in lung cancer. It can be useful for patients in whom tissue samples cannot be obtained due to technical reasons or a poor performance status.

Positive prognostic and predictive factors include the following: early stage of the disease, good performance status (Zubrod/ECOG score of 0–1 or 2), absence of clinically relevant weight deficit (a weight loss of no more than 5%), female sex [17].

The presence of activating mutations in the EGFR gene (exon 19 deletions and exon 21 mutation) and rearrangements in the ALK and ROS1 genes, have been reported to be predictive factors in treatment response to tyrosine kinase inhibitors (TKIs), but they are not recognised prognostic factors in survival, whichever treatment is used. Mutations in the EGFR gene are found in about 10–16% of adenocarcinomas in the European population and are unrelated to exposure to tobacco [18].

The presence of rearrangements in the ALK gene is associated with specific clinicopathological features, namely an earlier age at diagnosis in never-smokers and patients with a short history of smoking, and the histological type of the adenocarcinoma [19].

KRAS mutations are found in about 25% of patients diagnosed with adenocarcinoma of the lung. They are associated with smoking and are a negative prognostic and predictive factor in TKI treatment [20].

Other biomarkers, such as rearrangements in fusion genes, are being actively investigated as potential targets for new therapeutic technologies.

3. Screening in the United States, Europe and Poland

The aim of population screening programmes is to reduce mortality in the general population [21] by detecting the disease in its early, asymptomatic stage, in order to treat it effectively and, as a result, to prevent deaths from the disease. Activities aimed to prolong survival and to improve the quality of life, do not meet the definition of a population screening programme. However, the increasing possibilities of treatment interventions in patients with early-stage lung cancer, which can prolong survival and improve the quality of life, have triggered the development of screening programmes aimed to detect this malignancy in groups particularly exposed to risk factors, namely, in this case, to long and intensive smoking. The set of activities can be considered screening programmes for high-risk groups.

In the case of lung cancer, screening is intended for the asymptomatic subpopulation at a given age (over 50–55 years) with a determined minimum tobacco exposure (at least 20–30 pack-years, depending on the recommendations). These features define the high-risk group basing on the demonstrated dose-effect relationship between smoking and lung cancer [22].

According to some recommendations, additional risk factors (passive smoking, exposure to radon, environmental and occupational exposure to carcinogens, lung diseases not related to cancer, such as chronic obstructive pulmonary disease [COPD], idiopathic pulmonary fibrosis [IPF], a personal history of lung cancer or lung cancer in a first-degree relative) can also be taken into account when selecting the target group.

Screening programmes using conventional chest radiography conducted between 1950 and 1970 with or without sputum cytology, failed to show any statistically significant reduction in lung cancer mortality. This has been confirmed in a randomised phase 3 study (The Prostate, Lung, Colorectal and Ovarian — PLCO), which showed that annual screening assessments using chest radiography were useless in high-risk individuals [23].

Since the 1990s, low-dose computed tomography (LDCT) has been used as a screening tool. Chest LDCT is a safe non-contrast diagnostic procedure involving 10–30 fold lower radiation dose compared to standard CT examination. LDCT screening is intended to detect non-calcified nodules that may raise suspicion of lung cancer, depending primarily on their morphology and size, e.g. solid nodules; part-solid nodules; ground-glass nodules (GGNs). LDCT has a lower diagnostic value in non-solid nodules than in GGNs.

The thin-section of the reconstruction layer enables the detection of small lesions (high sensitivity), both benign and malignant [24, 25]. LDCT allows to evaluate other pathological lesions in the mediastinum, bronchi, lung parenchyma, blood vessels and upper abdominal structures visualised during the study.

Analyses of observational studies conducted in Japan, the United States and Germany have demonstrated that about 85–93% of stage I lung cancers can be detected using LDCT [26].

An international non-randomised study in over 31,000 high-risk individuals (I-ELCAP), has confirmed LDCT to be an effective tool for the detection of early lung cancer, with 85% of the cancers being detected in stage I. However, due to the short follow-up (40 months) and the low proportion of participants followed up for more than 5 years (only 20%), the projected 10-year survival rate of 92% was associated with a significant risk of statistical error [27].

The results of the National Lung Cancer Trial (NLST), the largest randomised clinical study that used LDCT for lung cancer screening versus chest radiography, that was published in 2011 and included over 53,000 participants, showed a 20% relative reduction in lung cancer mortality and a 7% relative risk decline in all-cause mortality, in the study group. On the basis of these results, the United States Preventive Services Task Force (USPSTF) recommends screening in the group at high risk of lung cancer, i.e. those over 55 years of age and a smoking history of at least 30 pack-years [28].

The results of the NLST have changed clinical practice. Since 2015, the Centres for Medicare and Medicaid Services (CMS) in the United States have covered the costs of LDCT in groups at increased risk of lung cancer. Reservations concerning the routine implementation of this screening, which have also been expressed by us, are mainly related to the high percentage of false positive results (positive results in at least one of the three rounds in 39.1% of the individuals), low cancer detection rate (only 3.5%), overdiagnosis

and overtreatment in the screened group.

A prospective randomised clinical study is currently under way in Europe (NELSON). It has enrolled over 15,000 current or former smokers with a smoking history of at least 15 pack-years, who undergo annual LDCT examinations [29]. While awaiting the publication of the study, European scientific societies, such as the European Society of Radiology (ESR), the European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) recommend screening as part of long-term programmes conducted in comprehensively equipped, multidisciplinary and certified centres [30, 31].

Another pilot study, the UK Lung Screening (UKLS), has confirmed the possibility of detecting lung cancer while it is still in the potentially curable stage [32].

The results of these two European studies may serve as proof of the efficacy of lung cancer screening using chest LDCT, unequivocally demonstrated in the American study, the NLST.

The Table 1 is presenting characteristics of the selected randomised controlled lung cancer screening trials.

Several Polish centres, including Gdansk, Szczecin, Warsaw, Poznan and Zabrze, have conducted pilot studies using chest LDCT in high-risk individuals. In total, almost 50,000 people were examined in the above-mentioned centres. Lung cancer was detected in approximately 1% of the examined individuals (from 0.86% in Szczecin, to 1.05% in Gdańsk). Lung cancer in stage I was 64 to 70% of detected cancers. The results of these studies have highlighted the scale of tobacco smoking in the Polish population, indicated the growing awareness of the risk of lung cancer in the society and confirmed the efficacy of LDCT in detecting pulmonary nodules [39, 40].

The decision to join a screening programme should be a shared decision made by the physician and a patient and should be individually discussed, particularly in patients with comorbidities.

4. Pathways for implementing lung cancer screening programmes in Poland and in Europe

No lung cancer screening programmes on a mass scale similar to those in the United States and China, have been implemented in Poland or in Europe. The guidelines on lung cancer screening based on LDCT are grounded on the assumption that such screening programmes or pilot projects will be implemented in Poland in the near future. Screening programmes using

LDCT have been recommended by the following documents prepared by European organisations and societies: the European Respiratory Society (ESR)/European Society of Radiology (ERS) white paper on lung cancer screening [30], the position statement of Swiss University Hospitals [41], the position statement of the European Society of Medical Oncology (ESMO) [42], the ESTS guidelines [31] and the British Thoracic Society guidelines [43]. In 2017, the European Union position statement on lung cancer screening has been published and recommended implementation of the low-dose CT screening throughout Europe as soon as possible [44]. Many countries (United Kingdom, Netherlands, Belgium, Denmark) are developing lung cancer screening programmes adapted to country-specific political, economic, epidemiological and cultural circumstances. Prepared by a multidisciplinary team of experts representing all the specialties involved in such programmes and having experience in conducting screening programmes, the document is intended to serve as a foundation for the preparation of a national programme for early detection of lung cancer.

In 2016, 269,000 people in Europe, including 22,000 in Poland, died from lung cancer, with late diagnosis being the main reason. The aims of the screening are early diagnosis, successful treatment and mortality reduction. Implementation of early lung cancer detection programmes on a mass scale is a high-priority task for healthcare systems in Europe and in Poland. A total of 4 pilot programmes have been conducted in Poland so far. All of them were short-term projects with only 1–3 screening examinations conducted in each participant. A total of about 50,000 people were screened in these programmes in Szczecin, Gdańsk, Poznań and Warsaw, with more than 500 cases of lung cancer being detected, most often in stage I, i.e. the stage in which curative surgery is still possible.

Public healthcare management institutions in Europe are awaiting the results of the randomised Dutch-Belgian study, NELSON, to be published in by 2019. Pathways for implementing the screening programmes within the European Community are bound to differ from country to country, depending on socioeconomic circumstances. Active steps need to be taken in Poland to prepare a cost-effective, high-quality programme for early detection of lung cancer. The launch of the programme should initially be restricted to centres with multidisciplinary teams experienced in conducting the types of projects and meeting the requirements of most guidelines published

Table 1. Characteristics of selected randomised lung cancer screening trials

Name of the study	Recruitment period	Enrollment criteria			Screening methods	Results of the screening programmes					
		Age	Pack-years	Years of quitting smoking		Number of screened individuals	LDCCT group	Control group	% of detected malignant neoplasms	% of lung cancer diagnosed at I TNM stage	
NLST [33]	2002–2004	55–75	≥ 30	< 15	Annual LDCT vs X-ray for 3 years	26,722	26,732	3.9%	3.5%	58.5%	30.7%
MILD [34]	2005–2011	> 49	≥ 20	< 10	Annual screen vs biennial screen for 5 years	1152	1151	3.6%	2.7%	52.4%	51.6%
		No cancers within past 5 years									
ITALUNG [35]	2004–2006	55–69	≥ 20	NA	Annual LDCT for 4 years vs no screen	1613	1593	4.2%	4.6%	36%	11%
DANTE [36]	2001–2006	60–75	≥ 20	< 10	Annual LDCT for 4 years vs no screen	1264	1186	5.2%	5.9%	71.2%	22.5%
		male									
DLCST [37]	2004–2006	50–70	≥ 20	< 10	Annual LDCT for 5 years vs usual care	2052	2052	4.9%	2.6%	50%	15.1%
		FEV ₁ > 30%, able to climb two flights of stairs without pausing									
NELSON [38]	2003–2006	50–75	≥ 15	NA	LDCT in year 1, year 2, year 4, and year 5–6 vs no screen	7557	NA	3.4%	NA	69%	NA
LUSI	2007–2011	50–69	NA	NA	Annual LDCT and smoking cessation for 5 years vs smoking cessation alone	2029	2032	3.1%	1.6%	74%	9.4%
		Heavy smoking history									
UKLS	2011–2014	50–75	NA	NA	Single LDCT vs no screen	2028	2027	2.1%	NA	66.7%	NA
		≥ 5% of 5-year lung cancer risk by LLP score									

by world organisations involved in screening programmes. The requirements are detailed in the next section. Basing on the experience gained by the centres, subsequent teams should be trained to conduct screening that provides the highest possible effectiveness and the lowest adverse effects for the participants.

In European countries, the implementation of lung cancer screening programmes will most likely be based on the experience gained in other screening initiatives implemented in the past (breast cancer, colorectal cancer). This means that these programmes will be in wholly or partly financed from public funding in order to give all the social groups of citizens equal access to the project [45].

5. Expected outcomes of screening implementation

The main goal of secondary prevention of lung cancer is to detect it at an early stage to reduce mortality associated with the malignancy. The ongoing studies in the United States and pilot projects in other countries, are aimed to develop a management algorithm leading to a significant reduction in side effects and adverse events associated with LDCT screening.

Observational studies have shown an increased detection rate in early stages of the disease (with about 85% of the detected cancers being stage I cancers), which entails considerably improved treatment outcomes in this group of patients [22].

In 2015, two American analyses were published that retrospectively reviewed data from the largest randomised screening programme, the NLST, using the Lung Imaging Reporting and Data System (Lung-RADS™) criteria [46, 47]. Basing on these studies, it was proposed to increase the threshold size for the pulmonary nodule to 6 mm, thus defining a positive result of chest LDCT. This change allowed to reduce the rate of false positive results from 27.6% to 10.6% in the study carried out by McKee *et al.* [46] and from 26.6% to 12.8% in the analysis performed by Pinsky *et al.* [47].

In an effort to standardise radiological guidelines for chest LDCT and to reduce false positive results in lung cancer screening, the American College of Radiology (ACR) eventually proposed a data classification and reporting system according to Lung-RADS™. It resembles other radiological classification systems, e.g. BI-RADS (Breast Imaging Reporting and Data System) approved

for breast cancer screening, PI-RADS (Prostate Imaging Reporting and Data System) used for the diagnosis of prostate cancer or LI-RADS (Liver Imaging Reporting and Data System), helpful in the diagnosis of hepatocellular cancer.

In practice, there are several protocols defining the conditions of lung cancer screening and algorithms to follow if nodules or other suspected pulmonary lesions are detected.

6. Risks and problems associated with the implementation of screening programmes

Prognosis in lung cancer strictly depends on the initial stage of the disease at diagnosis. The 5-year survival rates in non-small cell lung carcinoma (NSCLC) are as follows: 49% and 45% in stages IA and IB, 30% and 31% in stages IIA and IIB, and 14% and 5% in stages IIIA and IIIB, respectively. Only about 1% of NSCLC patients with stage IV disease survive 5 years after diagnosis [48].

In the NLST, 40% of the lung cancers were in stage IA, 12% in stage IIIB and 22% in stage IV. The respective proportions in the control arm, the chest radiography arm, were 21%, 13% and 36%. The proportion of lower-stage cancers is therefore increasing, as is the proportion of lobectomies versus pneumonectomies (1% in screening studies versus 20–30% of pneumonectomies in symptomatic patients) [49].

The drawbacks of screening in lung cancer include the following:

1. Detection of clinically irrelevant lesions, among them indolent lung cancers; there is still an unmet need for effective tests that would assist in differentiating between malignant and benign nodule phenotypes (molecular screening, immunological evaluation, state-of-the-art techniques in nuclear medicine and radiology etc.).
2. A negative psychosocial repercussion among people who do not accept the idea of living with a pulmonary nodule in their bodies (where management according to the algorithm guidelines is not required).
3. The need to use invasive diagnostic methods, which expose the patient to potential side effects.
4. The risk of unnecessary surgery (surgical treatment of non-cancerous nodules).
5. The risk of delayed treatment of lesions suggestive of a benign nature (management according to the algorithm imposing specific time intervals during observation of the nodule).

6. Suppression of vigilance in smokers: “since there are tests now that can detect lung cancer early, I don’t need to quit smoking”.
7. High costs of detecting one cancer case among the screened individuals (about PLN 30,000 in Poland and much more in Europe and the United States).

LDCT screening identifies both malignant and benign non-calcified nodules. While the overall proportion of false positive results in the study group of the NLST was high (96.4%), the cumulative risk of a false positive result was 33% in individuals undergoing screening in two consecutive annual scans. The use of LDCT in the NLST was therefore characterised by a high sensitivity and a relatively low specificity. The use of volumetric analysis for the assessment of pulmonary nodules in the NELSON study is likely to significantly decrease the proportion of false positive results [50].

The categorisation and reporting of the detected lesions can be inconsistent. Therefore, there is a need to rationalise and unify the diagnostic algorithms used so far. In an effort to reduce the number of false positive results in lung cancer screening, the American College of Radiology (ACR) proposed a data classification and reporting system according to Lung-RADS™ based on approaches adopted in other cancers.

The use of LDCT as a screening tool is associated with detecting a relatively high proportion of pulmonary nodules in the screened population (an average of 20%), most of which will turn out to be benign. The additional investigations that the volunteers must undergo, increase their exposure to ionising radiation and may also involve additional invasive procedures.

Despite a relatively low dose of radiation used in the screening (approximately 1.5–2 mSv per examination), the radiation dose increases to 8 mSv and 14 mSv if the lesions identified by LDCT require further evaluation by diagnostic CT or PET-CT, respectively. On the basis of the NLST, it has been estimated that the cumulative radiation dose absorbed during 3 years of lung cancer screening is about 8 mSv (including both screening and diagnostic scans).

The influence of radiation exposure on the risk of inducing another carcinoma was extensively studied in lung cancer screening programmes. Rampinelli *et al.* [51], analysed the results of the COSMOS programme, in which over 5,000 people were subjected to low-dose CT screening. During the 10 years of the programme

implementation, over 40,000 LDCT studies and over 600 PET-CT examinations were carried out. The reported risk of radiation-related cancer was approximately 0.05%. Due to the significant impact of the LDCT screening on reducing mortality from lung cancer, it was considered as an acceptable risk.

In the NLST, the proportion of invasive non-surgical procedures in patients with benign lesions was high (73%). In terms of unnecessary operations, the proportions were 1.2% for biopsies and bronchoscopies, and 0.7% for mediastinoscopies and thorascopies [33].

The largest number of overdiagnoses in screening programmes has been reported for breast cancer, prostate cancer and, more recently, for lung cancer screening with LDCT. Overdiagnosis refers to the detection of subclinical lesions or indolent tumours that do not cause symptoms and will not decrease the patient’s life expectancy. Detection of such lesions may result in unnecessary diagnostic procedures and treatments, psychological burden associated with patient awareness of the disease, and certain economic consequences. Overdiagnosis may unjustifiably inflate curability and survival statistics. In the NLST, the proportion of indolent tumours has been estimated at over 18% [52].

The effect of LDCT screening on the quality of life is unclear. In the NLST and the NELSON study, the quality of life assessment was conducted in patients undergoing the screening.

Among the participants of the NLST, including those with false positive results, no increased rate of anxiety or any differences in the quality of life were observed 1 and 6 months after the end of the screening [53].

In the NELSON study, about 88–99% of the screened patients did not report any negative effects of the screening, although 46% reported distress associated with the wait for the results. No differences in the quality of life were, however, observed during 2 years [54].

It has been suggested that participation in a screening programme may provide the participants with false reassurance and a reason for continuing to smoke. Active smoking cessation counselling should be an integral part of any screening programme.

7. Requirements for screening centres: the multidisciplinary team

A Lung Cancer Screening Centre will be a centre providing high-quality medical services

and must meet the highest quality requirements in the implementation and effective conduct of recruitment among individuals at high risk of lung cancer, in the performance of LDCT scans, the correct interpretation of the scans, and the provision of standard instructions regarding further follow-up or evaluation and effective treatment of patients diagnosed with lung cancer. The Centre should have specialists in all the relevant fields who will work in a multidisciplinary team (MDT) and determine each diagnostic and therapeutic step during MDT meetings. The Lung Cancer Screening Multidisciplinary Team (LCS-MDT) should be composed of a radiologist, pathologist, pulmonologist, thoracic surgeon, oncologist, nurse and a co-ordinator experienced in the diagnosis and treatment of lung cancer and in programmes for early detection of lung cancer. All the members of the LCS-MDT must be specialists in the respective fields and specialise in the diagnosis, treatment and long-term follow-up of nodules identified in screening. Their knowledge should be based on the most recent standards and publications related to lung cancer screening [55]. The LCS-MDT should provide the programme participants with the model of lung cancer diagnosis and treatment commensurate with the adopted standards and recommendations cited in the present document. In addition to the above, the Centre must maintain the appropriate level of provision of information to the participants regarding the adopted procedures, and the standards related to uniform data acquisition and subsequent collection in the general access system in accordance with the Polish Society of Cardiothoracic Surgeons recommendations [56, 57].

A physician specialising in the treatment of tobacco dependence should be an integral member of the LCS-MDT [58] committees with expertise in lung cancer screening were assembled by the Thoracic Oncology Network of the American College of Chest Physicians (CHEST). A tobacco dependence treatment programme will reduce lung cancer mortality and significantly affect the cost effectiveness of the programme for early detection of lung cancer [59, 60]. All the participants of the programme should have access to a smoking cessation programme, as part of the services provided by the public healthcare system. Data on smoking and on the results of cessation interventions should be collected in the general access system and cyclically analysed [61].

Each implemented programme for early detection of lung cancer should provide the data on

the diagnosis and treatment of its participants to a central registry. Efforts should be made to collect biological samples from all the participants of such programmes, with the view of conducting molecular testing with central registration within a biobanking network.

8. Radiological requirements for the equipment, absorbed dose and nodule evaluation

An effective screening programme requires establishment of a qualified multidisciplinary team whose radiologists will ensure that the radiation doses are kept to the minimum, while preserving sufficient quality of the scans to be able to assess the size and morphology of any focal lesions and categorise the lesions according to Lung-RADS and/or volumetry measurements recommended by Henschke *et al.* already in 1999 [62, 63], then validated and further developed in Nelson trial [50] and UKLS trials [32].

It is advisable that the radiologist's work is complemented by the use of computer software detecting focal lesions in the lungs, measuring their sizes and volumes, calculating their volume doubling times and comparing their sizes. Continued education of the staff and site accreditation will contribute to an increased effectiveness of the screening programmes.

The diagnostic efficacy of chest LDCT, compared to chest radiography, is four-fold higher in detecting malignant lesions and about six-fold higher in identifying stage I lung cancer [64]. LDCT is, however, associated with a higher proportion of false positive diagnoses requiring invasive diagnostic procedures that are performed on the basis of LDCT (7% vs 4% of all participants) [65].

The European Society of Radiology (ESR) and the European Respiratory Society (ERS) published a joint report in 2015 on early detection of lung cancer in Europe, while we are still awaiting the final results of the largest randomised controlled study in Europe, the Dutch-Belgian NELSON study (*Nederlands-Leuvens Longkanker Screenings Onderzoek*), in which almost 16,000 current or former smokers were screened between 2003 and 2006. The report emphasises that the results of the NLST, a study conducted according to a very good methodology, cannot be ignored, and recommends using LDCT as a screening tool in research studies or clinical practice in certified multidisciplinary centres [30].

There are several reasons for the recommendation for having only dedicated centres conduct screening. Radiologists are responsible

for ensuring that the radiation dose is kept to the minimum, for having a team of qualified members with experience in the assessment of low-dose scans, for participating in training and for using specific radiological assessment criteria.

The most recent guidelines concerning CT scanners published by the American College of Radiology and the Society of Thoracic Radiology (ACR-STR), partially due to their modest requirements, recommend the use of spiral scanners with at least 16 detector rows and following the “as low as reasonably achievable” (ALARA) principle [66].

While following the ALARA principle, LDCT examinations should be carried out in a way that enables radiologists to establish the diagnosis on the basis of an acceptable image quality while using the lowest possible radiation dose. Reconstruction algorithms play a significant role in reducing the radiation dose. The iterative dose reduction system and the use of multiple-row detector technique (with 128 or more detector rows) in the latest CT scanners may reduce the effective dose to 0.1 mSv [67]. According to ACR-STR, the maximum absorbed dose during LDCT should not exceed 3 mGy in the standard patient (height 170 cm, weight 69.75 kg) [66]. The absorbed doses in the NLST and the NELSON study ranged from 2.5 to 6 mGy at the effective doses of 1 mSv in men and 1.3 mSv in women [68].

The LDCT examination must include images from the lung apices to the costophrenic angle. Scans are obtained in deep inspiration without administration of intravenous or oral contrast. The maximum slice thickness is 2.5 mm with the recommended value of 1 mm.

Ready-to-use protocols for CT scanners from various manufactures have been prepared and are available on the American Association of Physicists in Medicine website [69].

According to ACR-STR, the radiologist involved in screening tests must be experienced in analysing low-dose examinations with a documented evaluation (interpreting) of at least 300 chest LDCT examinations in the past 36 months [70]. Image analysis should be performed on dedicated diagnostic consoles in order to detect early lung cancer (nodule) and not to miss any significant lesions. Maximum intensity projection (MIP) reconstructions should be used for pulmonary nodule detection [71]. The examination should be evaluated in the pulmonary window scan by scan. The use of a standard window for soft tissue is additionally recommended to identify any calcifications or enlarged lymph nodes, bearing in mind that

their assessment in a low-dose scan is limited. Any additional significant findings should also be reported, such as emphysema and other lung diseases, atherosclerosis, including the coronary artery calcification (CAC) score, aneurysms, osteopenia and other renal, adrenal, hepatic and breast pathologies. All the detected nodules should be classified into one of the following four categories:

- Solid nodules: nodules that completely obscure the lung parenchyma.
- Part-solid nodules: nodules with fragments that do not obscure the lung parenchyma.
- Ground-glass nodules (non-solid nodules): nodules that do not obscure the lung parenchyma.
- Calcified nodules.

Follow-up scans should be compared with baseline scans, and in the first round of the screening programme a check for any prior chest CT examinations should be undertaken; and if such examinations were carried out previously and nodules are detected on screening, a comparative analysis of size and volume based on the findings is recommended.

The nodule size is measured in the pulmonary window on images acquired in the transverse plane (not on coronal or sagittal reconstructions) in various axes. The mean size of the nodule should be calculated from the longest and shortest dimensions and from indirect measurements. The use of computer-assisted detection (CAD) systems and volumetric analyses is advised, which assists the radiologist in visualising the lesions and decreases incongruent differences between the observers' descriptions. In the case of follow-up examinations, these systems allow to compare nodule volume (volumetric assessment) [72] they do not only provide a numerical value but also the volume doubling time (VDT).

In the Dutch-Belgian NELSON study, nodule volume was a useful indicator of malignancy: nodule volume changes of 25% over 3 months suggested potential malignancy. In Europe, volumetric criteria based on the results of Nelson trial are accepted by the majority of radiologists involved in screening. Volumetric analysis according to these criteria is recommended, both in the first and the control LDCTs, in all non-calcified nodules suspected of malignancy.

In the first NELSON protocol, cut-off values for positive/negative result were 50 and 500 mm³ respectively, and in all cases within this range, control LDCT was scheduled in the period shorter than 12 months. Retrospective analysis showed, however, that small nodules of < 100 mm³

(< 5 mm in diameter) were associated with a low risk of malignancy and control LDCT in these cases was the same as in the population without any nodules [73, 74]. Nodules $\geq 300 \text{ mm}^3$ in volume ($\geq 10 \text{ mm}$ in diameter) required further evaluation: a biopsy or PET-CT. In patients with intermediate nodules with volume 100 mm^3 to 300 mm^3 (5–10 mm), the control was performed after 3 months with VDT measurement [73]. In patients with VDT of 400–600 days, lung cancer was estimated as intermediate and further decisions were discussed on MDT. In patients with nodules where VDT was > 600 days, very low lung cancer risk was assessed. Any new nodules on control LDCT with volume of $30\text{--}200 \text{ mm}^3$ (4–8 mm in diameter) were considered as suspicious and a checkup after 3 months was performed in these cases. When VDT was < 600 days in such a new nodule, diagnostic procedures were implemented like in all nodules on baseline LDCT > 200 mm^3 [74].

In solid lung nodules, a radiologist should always analyse and consider their structure that may be for example typical of intraparenchymal lymph nodes, lymph nodes located close to interlobar or intersegmental planes or additionally, inflammatory nodules where the evaluation should be based not only on size measurement but should include the analysis of nodule morphology [75, 76].

In pure and partsolid GGO (Ground Glass Opacity) nodules, the observation should always be considered to avoid invasive diagnostic procedures. In the observation of growth, analysis and morphology assessment is crucial for malignancy risk assessment [75, 76]. In such a nodule the control is performed every 12 months if any previous CT is available. In newly diagnosed GGO lesions checkup after 3 months should be performed and subsequently after 12 months if malignancy risk is < 10%. When the risk is > 10%, invasive diagnosis or operation should be considered.

According to the NELSON study, malignant tumours detected by LDCT are more frequently located in the upper lobes and on the lung periphery [29].

The criteria indicating a benign nature of a nodule with an acceptable diagnostic effectiveness are calcifications and fat, while the growth of a nodule with a volume doubling time in the range of 20–400 days indicates malignancy. Two-thirds of smokers are diagnosed with nodules, 95% of which are less than 10 mm in size with 3% of them being malignant [33].

Evaluation of the nodule structure requires clinical experience. In addition to volumetric assessment, lesions measuring 10 mm or less may also be evaluated using the Lung-RADS criteria

developed by the ACR to standardise the reporting of screening LDCT examinations [46].

Category 1 (< 1% risk of malignancy) comprises nodules with the following benign features:

- Completely calcified nodules.
- Nodules with central, concentric or popcorn-like calcifications or fat-containing nodules.

Category 2 comprises benign lesions with a low risk of malignancy (< 1%):

- Solid nodules with an average diameter of < 6 mm, or new nodules (appearing on a subsequent scan) with an average diameter of < 4 mm.
- Part-solid nodules with an average diameter of < 6 mm on the baseline scan.
- Ground-glass nodules with an average diameter of < 20 mm, or $\geq 20 \text{ mm}$ if slowly growing or stable during the follow-up period.
- Category 3 and 4 nodules if unchanged for at least 3 months.

Category 3 comprises probably benign lesions with 1–2% risk of malignancy and includes as follows:

- Solid nodules with an average diameter of $\geq 6 \text{ mm}$ and < 8 mm, and new solid nodules with an average diameter of $\geq 4 \text{ mm}$ and < 6 mm.
- Part-solid nodules with an average diameter of $\geq 6 \text{ mm}$ and a solid component of < 6 mm, and new part-solid nodules < 6 mm.
- Ground-glass nodules larger than 20 mm on the baseline scan or new.

Category 4 comprises potentially malignant nodules and includes three subcategories: 4A, 4B and 4X.

Category 4A (5–15% risk of malignancy) comprises the following:

- Solid nodules with an average diameter of $\geq 8 \text{ mm}$ and < 15 mm on the baseline scan, and growing nodules < 8 mm, and new nodules with an average diameter of $\geq 6 \text{ mm}$ and < 8 mm.
- Part-solid nodules with an average diameter of $\geq 6 \text{ mm}$ and a solid component of $\geq 6 \text{ mm}$ and < 8 mm, and new or growing part-solid nodules with a solid component of < 4 mm.
- Endobronchial nodules.

Category 4B is associated with a risk of malignancy exceeding 15% and includes as follows:

- Solid nodules with an average diameter of $\geq 15 \text{ mm}$, and new or growing nodules of $\geq 8 \text{ mm}$.
- Part-solid nodules with a solid component of $\geq 8 \text{ mm}$, and new or growing nodules with a solid component of $\geq 4 \text{ mm}$.

Category 4X is associated with a risk of malignancy exceeding 15% and comprises category 3 and 4 nodules with additional features suggestive of malignancy, such as:

- spiculations,
- ground-glass nodules with a volume doubling time of one year,
- enlarged regional lymph nodes.

Category 1 and 2 nodules should be followed up annually by LDCT. Category 3 nodules require a follow-up LDCT in 6 months. The recommended management of category 4 nodules involves a follow-up LDCT in 3 months, a biopsy or a PET-CT of lesions with a solid component of > 8 mm.

When evaluating a nodule using the Lung-RADS criteria, the measurements should be performed on lung windows and reported as the average diameter rather than the longest diameter (similarly to the reporting of cancer lesions using the RECIST classification). For nodules visually assessed as round, no additional measurements need to be performed. The increase in lesion size should also be defined more precisely and nodule growth is defined as an increase in size of ≥ 1.5 mm.

Lung-RADS systematises the assessment of nodules identified in LDCT for the purpose of early detection of lung cancer. It is currently a standard method used for the assessment of pulmonary nodules in the participants of screening programmes in the United States. It can be easily implemented in Poland. On the other hand, in Europe, after the publication of selected results of the NELSON trial, emphasis is placed on volumetric assessment, which is a very accurate method but only when performed in experienced centres.

9. Population at risk and risk assessment

In February 2015, the LDCT lung cancer screening programme was implemented in the United States. Out of approximately 8.5 million eligible individuals, a total of about 1.5 million subjects were included until December 2016 (personal communication: Dr Christine D. Berg, NCI, USA).

Due to methodological and financial reasons and a strong association of the malignancy with smoking, the programme for the detection of early lung cancer does not cover the entire population [30, 77], but only the subpopulation of individuals at an increased risk of developing the disease, defined by specific age and tobacco exposure.

Fundamental to the screening programme intended for the high-risk population is the correct selection of the target group, whose characteristics will depend on epidemiological data, medical circumstances and the level of financial funding.

In the NLST study and in the USPSTF recommendations, inclusion criteria for the screening

programme were based on the number of pack-years and the age of the enrolled individuals [33]. Currently, after re-analysis of the NLST and PLCO cohorts, it is recommended to use predictive models of individual risk of developing lung cancer, which are based on additional risk parameters, that allows to target more precisely the screening population [30, 47, 74]. The application of the models determining probability of tumour malignancy in a given person is an additional recommended element increasing the number of true positive results [31, 43]. Nevertheless, determining the target population of lung cancer screening programmes remains a complex and empirical problem related to the fact that the occurrence of lung cancer in a particular person is a multidimensional variable, similar to the trajectory of health. The predictive model appropriate for the American population not necessarily is appropriate for the Polish population because of their differentness, heterogeneity and dissimilar response to various factors that are determined by environmental influence.

Evaluation of the CT scans should be performed according to criteria specifying how the size of the pulmonary nodule (SPN) should be measured and defining which results should be considered positive and which should be treated as false positive. All these methodological considerations translate into the sensitivity and specificity of LDCT in detecting early-stage lung cancer and determine its cost and other financial performance measures [78].

In the past two decades, considerable progress has been made in the selection methods, in the modelling of the risk group screened with LDCT and in the interpretation of CT scans. This allows the reduction of the number and frequency of examinations in the programme and limits unnecessary diagnostic procedures.

A positive LDCT result is defined as a non-calcified solitary pulmonary nodule (SPN) having a specific diameter or volume. Pulmonary nodules measuring 2 mm in diameter or smaller are observed on CT scans in most adult individuals [79]. In the NLST, the proportion of positive results, i.e. all nodules measuring 4 mm or larger, was 27% [33]. This is several times higher than that in the NELSON study (2.7%), in which the nodules were assessed volumetrically [30]. In the latter study, however, a broad category of indeterminate nodules ($50\text{--}500\text{ mm}^3$) was distinguished, that were not included in the positive results [77], and secondly, the mortality reduction data was not published.

A repeat analysis of the I-ELCAP and NLST results [47, 80] has shown that the nodule size that requires a follow-up LDCT sooner than after one year, may be bigger than initially assumed in the NLST.

False positive results account for a considerable proportion of the detected nodules, as only 1–4% of them are early-stage lung cancers [30, 77].

The following methods are used to reduce the number of false positive results:

1. Assessment of risk factors: According to the National Comprehensive Cancer Network (NCCN) standards, risk factors include as follows: smoking, exposure to radon, occupational exposure (e.g. silica, heavy metals, soot, asbestos), personal history of cancer (e.g. head and neck cancer in the past), lung cancer in first-degree relatives, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) [81].
2. If one additional risk factor is present, the parameters of the target group are lowered from age 55 years and tobacco exposure of ≥ 30 pack-years, to age 50 years and tobacco exposure of ≥ 20 pack-years [81].
3. Use of prediction models: With the use of linear regression equations that include the above elements and socioeconomic data, it is possible to estimate the individual risk of developing lung cancer resulting from the characteristics of the population of concern [81, 82]. Only three of many prediction models have provided a more accurate selection of individuals for screening, compared to the criteria used in the NLST [83]. Furthermore, models that take into account the patient's clinical details and the morphological features of the nodule, can determine the degree of probability of the nodule being malignant [76]. Both classes of the prediction models are a great help in individual qualification of subjects for inclusion in a screening programme (shared decision-making), particularly when discussing the benefits and side effects of the programme procedures being planned.
4. Advanced image analysis: radiomics, i.e. the evaluation not only of the morphological (semantic) but also the indescribable (agnostic) parameters, which better characterise the imaged tissue [84].
5. Determination of genomic or protein biomarkers obtained from the serum, which confirm (positive predictive value) or, in a certain configuration, exclude (negative predictive value) the presence of cancer in the screened patient [85–87].

According to epidemiological data, only 10% of lung cancers occur before the age of 55, while 56% of the cases are found in the 55–74 age group [88]. The remaining 32% are found in patients aged 75 or older.

Determination of the target population is of key importance for the cost effectiveness of the screening programme and the desired improvement in the detectability of early lung cancers [89].

The scenario defined as A-55-80-30-15 (where the letter A signifies annual screening, the numbers “55” and “80” signify the age of starting and ending the screening, respectively, the number “30” refers to tobacco exposure expressed in pack-years, and the number “15” indicates the longest period since smoking cessation) has proved optimal in terms of the balance between the costs (largely the costs of LDCT scans and medical consultations) and the number of lung cancers detected and the number of adverse events that occurred as a result of diagnostic and surgical procedures [90]. The tested prediction models were calibrated on the basis of the NLST and PLCO study results. The above scenario was optimal compared to the 120 scenarios characterised by the variables described above whose values were modified. LDCT performed every 3 years, every 2 years and every year was shown to reduce lung cancer mortality by an average of 6%, almost 10% and about 20%, respectively. In a given scenario, the number of follow-up LDCT examinations and the number of false positive results increases with the number of baseline examinations. For example, a reduction in the number of pack-years to 20 and an increase in the duration of the period since smoking cessation to 25 years (the A-55-80-20-25 scenario) results in a 58% increase in the number of LDCT examinations and a 26% increase in the number of new cases detected. The number of LDCT examinations needed to prevent 1 death of lung cancer increased from 550 to 685 cases (24%). Among all the effective scenarios, the annual LDCT in patients aged 55 to 80 shows a marked benefit while preserving a moderate level of side effects [90]. The results of the analyses and simulations related to the modelling of the population that benefits the most from the lung cancer screening programme using LDCT, have been taken into consideration to the greatest extent in the NCCN recommendations.

The recommendations for inclusion based on the stratification of lung cancer risk are as follows:

1. Individuals aged 55 to 74 with tobacco exposure of at least 20 pack-years and the non-smoking period of no more than 15 years.

2. Individuals aged 50 to 74 with tobacco exposure of at least 20 pack-years, the non-smoking period of no more than 15 years with one of the following risk factors:

- Occupational exposure to silica, beryllium, nickel, chromium, cadmium, asbestos, arsenic compounds, diesel engine fumes, coal combustion fumes, and soot.
- Exposure to radon.
- Personal history of cancer: lung cancer survivor, a history of lymphoma, head and neck cancer or smoking-related cancers, e.g. bladder cancer.
- Family history of lung cancer in a first-degree relative.
- History of lung diseases: chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF).

A high-risk individual is included in the programme based on a shared decision made by the subject and their healthcare provider (shared decision-making), who discusses with the individual the principles of the screening programme, the benefits and the side effects of the method based on the following:

- The prediction model by Tammemägi: the lung cancer calculator PLCOm2012.
- The prediction model for the malignant features of a nodule (McWilliams (PanCan) model) [76].
- Information materials similar to those offered by the Agency for Healthcare and Research Quality (AHQR) [91].

The interpretation of LDCT findings (the definition of the positive result) and further recommendations are in line with the Lung-RADS included in the screening recommendations NCCN v.1.2017 (see the next paragraph).

3. Definition of the false positive result: a solitary pulmonary nodule that requires LDCT and/or diagnostic and surgical procedures within less than one year, and is not an early lung cancer.
4. An individual who meets the programme inclusion conditions may become its participant if they give consent to undergo invasive diagnostic procedures and; possibly, surgery.
5. An individual included in the programme remains its participant as long as they remain a candidate for treatment with a curative intent.

The A-55-80-30-15 screening scenario turned out to be optimal for economic and medical reasons, i.e. indicated the group in which the allocation of funds in the NLST and PLCO cohorts were the most effective [90]. Taking into account

the over-normative air pollution in Poland and epidemiological data [8], the team of experts proposes the initial scenario A-55-74-20-15, with a reduction of age in the case of an additional risk factor in accordance to the NCCN recommendations. Then, the screening scenario of the target population takes the form of A-50-74-20-15. Cautious estimates indicate that the number of people who meet the inclusion criteria for screening amounts to around 2 million in Poland. Assuming that the cost of LDCT examination with a radiological report and a medical appointment is PLN 300, the estimated cost of the examination of the entire population with increased risk would exceed PLN 600 million.

Annually, about 21 thousand persons is developing lung cancer [8], of which only 17% is undergoing surgical treatment, i.e. in an early (local or loco-regional) stage (Polish National Lung Cancer Registry). Lung cancer screening programmes would most likely increase the percentage of surgically treated cases [27, 28, 30], which are more cost-effective. In the near future, a financial amount can be expected to allow screening 3-5% of the target population.

10. Smoking cessation programme

From the participant's point of view, lung cancer screening is often the first significant intervention that prompts reflection on how smoking affects health. Participants of the screening programme receive a lot of information and signals whose perception and psychological effects on behaviour and decisions have not been fully studied [92].

The risk that lung cancer screening may be treated by its participants as an alternative to smoking cessation to reduce mortality, has been recognised and confirmed by many authors [93].

Social determinants of tobacco dependence come down to the wider propagation among individuals with lower economic status, education level or social rank. As a result, both the awareness of the harmful effects of smoking and of the possibility to receive support is lower than that among the middle class representatives [94].

The costs of adding a cessation intervention to an LDCT lung cancer screening programme increase the total cost by a few to over a dozen percent. At the same time, the cost effectiveness as measured by quality-adjusted life years gained increases 1.7- to 5.4-fold [95].

It is therefore beyond any doubt that combining screening with cessation intervention is justified. There is still the problem of designing

the entire intervention in a way to ensure that the percentage of sustained quitters is significantly lower and the relapses are less frequent compared to spontaneous smoking cessation, because the analysis of practical interventions reveals that this is not always possible to achieve [96].

It is also advisable to consider the assessment of lung age conducted in all the participants, given the linear relationship between the lifetime number of cigarettes smoked and pulmonary function, and the strong correlation of lung cancer and COPD [97, 98], and to more actively recruit individuals from economically and/or socially disadvantaged groups to undergo screening.

We propose the following pathway for smoking cessation intervention as part of the screening programme:

I. Allocation to specific intervention paths.

Patients being considered for LDCT screening are allocated to one of the following three groups on the basis of their declarations: active smokers, former smokers-abstinent for less than 12 months, and former smokers-abstinent for more than 12 months. By joining the LDCT screening programme, the participants agree to the cessation intervention.

II. Active smokers during the screening programme undergo the following diagnostic evaluations:

- A standardised interview to assess smoking intensity and the severity of dependence (Fagerström).
- A test of motivation for smoking cessation (Schneider).
- Measurement of exhaled carbon monoxide (Smokerlyzer) or salivary cotinine.
- An assessment of depression (Beck's scale).

On the basis of the above evaluations, patients are provided with appropriate support in the form of consultation, psychotherapy sessions and education. Pharmacological support includes nicotine replacement therapy as the first-choice treatment, and cytisine, varenicline and bupropion if previous treatment failed or if the patient has absolute or relative contraindications to nicotine-containing products. Patients with a positive evaluation of depression are advised to register at an outpatient psychiatric facility.

III. Patients declaring abstinence from smoking for less than 12 months undergo Smokerlyzer testing (or cotinine testing, if Smokerlyzer testing is not possible) and if their non-smoking status is confirmed, they take a test measuring their motivation to continue not to smoke and undergo a short intervention reinforcing their decision to quit smoking.

IV. Patients declaring abstinence from smoking for more than 12 months receive a consultation to reinforce their motivation to maintain the non-smoking status.

V. All the individuals being considered for the screening programme are asked about the exposure to passive smoke in their workplace or at home. If such exposure is identified, an invitation is extended via the patient to the patient's relatives and co-workers to participate in the cessation intervention.

11. Evaluation and treatment of lesions detected on screening examinations

One of the most important topics related to the conduct of programmes for early detection of lung cancer using LDCT is the implementation of a detailed algorithm for the diagnosis and treatment of the detected nodules, as most of these nodules are benign [55]. The risk of overlooking early lung cancer must be minimised, while meeting the criteria for high specificity of the management in order to limit the unnecessary invasive diagnostic and therapeutic interventions [39, 99]. It is very important in this context to use the new pathological classification system for adenocarcinomas and its correlation with the radiological appearance of the nodules [100, 101].

The size of the nodule and its characteristics play a significant role in deciding the further course of action and determines whether the individual will undergo observation, invasive diagnostic evaluation or treatment [101]. One-dimensional measurement of the nodule diameter is recommended. Data on the use of volume measurement and the volume doubling time (VDT) are very promising but require further evaluation [50, 102]. Adoption of the lower value of the diameter is of fundamental significance for the sensitivity of screening, and hence the proportion of false positive results [103].

There is currently no commonly accepted testing protocol related to a procedural algorithm in all the guidelines. We propose to follow the Fleischner Society guidelines, adopted by the National Cancer Comprehensive Network for studies of early detection of lung cancer [81, 104, 105]. Nodules detected on LDCT require further evaluation based on the category they are assigned to by the radiologist: solid, part-solid or non-solid. According to the National Comprehensive Cancer Network guidelines, nodule assignment should be based on the analysis of the radiological image according to the guidelines of the American College of Radiology Lung (RADS) [46, 106]. The

management in each of the category is based on the nodule size.

Solid nodules

Nodules < 6 mm (Lung-RADS category 2, probability of lung cancer < 1%) require a repeat LDCT after 12 months until the risk of malignancy is excluded.

Nodules 6–7 mm (Lung-RADS category 3, probability of lung cancer 1–2%) require a repeat LDCT after 6 months.

Nodules 8 to 14 mm (Lung-RADS category 4A, probability of lung cancer 5–15%) require a repeat LDCT after 3 months or consideration of PET-CT, which is one of the many diagnostic methods available for lung cancer detection. The sensitivity of PET-CT for nodules < 8 mm is insufficient to consider this modality a routine diagnostic procedure [102].

Nodules ≥ 15 mm (Lung-RADS category 4B, probability of lung cancer > 15%) require chest CT with contrast and/or PET-CT.

Endobronchial nodules require a repeat LDCT after 1 month or directly after an episode of acute cough. In the case of equivocal findings, flexible bronchoscopy should be performed.

Patients who have undergone PET-CT should be managed as follows:

Where there is low suspicion of lung cancer, LDCT after 3 months is recommended.

Where there is high suspicion of lung cancer, a fine-needle biopsy is recommended with aspiration of an adequate amount of material for histological and molecular examination [102, 104], or surgical resection of the nodule. Where the biopsy rules out malignancy, the patient should undergo LDCT after 12 months of observation.

Part-solid nodules

Nodules < 6 mm (Lung-RADS category 2, probability of lung cancer < 1%) require a repeat LDCT after 12 months until the risk of malignancy is excluded.

Nodules ≥ 6 mm with solid component < 6 mm (Lung-RADS category 3, probability of lung cancer 1–2%) require a repeat LDCT after 6 months.

Nodules ≥ 6 mm or with solid component 6–7 mm (Lung-RADS category 4A, probability of lung cancer 5–15%) require a repeat LDCT after 3 months or consideration of PET-CT.

Nodules with solid component ≥ 8 mm (Lung-RADS category 4B, probability of lung cancer > 15%) require chest CT with contrast and/or PET-CT.

Patients who have undergone PET-CT should be managed as follows:

Where there is low suspicion of lung cancer, LDCT after 3 months is recommended.

Where there is high suspicion of lung cancer, a fine-needle biopsy is recommended with aspiration of an adequate amount of material for histological and molecular examination [102, 104], or surgical resection of the nodule. Where the biopsy rules out malignancy, the patient should undergo LDCT after 12 months of observation.

Non-solid nodules

Nodules < 20 mm require observation and LDCT after 12 months until the risk of malignancy is excluded.

Nodules > 20 mm require a repeat LDCT after 6 months.

For solid, part-solid and non-solid nodules, appropriate management protocols are used in the follow-up of the detected lesions.

Treatment of early lung cancer detected on screening follows the guidelines on the treatment of lung cancer adopted by the Polish Oncology Union. **Selected aspects related to non-solid nodules are discussed in the section on the recommendations for surgical treatment.**

12. Pathology

Lung cancers include a group of non-small-cell lung carcinomas, which account for about 85% of all primary lung cancers, with the remaining 15% being small-cell lung carcinomas [107]. Among the histologic types of non-small-cell lung carcinoma, adenocarcinoma is the most common (approx. 43.2%), followed by squamous cell carcinoma (approx. 22.8%) [108].

The WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart published in 2015 introduces the principles of lung cancer diagnosis using small biopsies and cytology and proposes a new classification of adenocarcinoma [109]. The term bronchioloalveolar carcinoma (BAC) has been replaced by the following terminology:

- adenocarcinoma in situ (AIS),
- minimally invasive adenocarcinoma (MIA),
- invasive adenocarcinoma [109, 110].

Adenocarcinoma in situ and minimally invasive adenocarcinoma usually refer to a solitary lesion or, less frequently, to multifocal lesions measuring ≤ 3 cm in diameter characterised by the lepidic pattern on microscopic examination.

In AIS, no stromal or pleural invasion and no tumour cell emboli in blood and lymphatic vessels are observed, while MIA is characterised

by the presence of small foci of invasion ≤ 0.5 cm in diameter in a single field. Invasion is defined as the presence of a non-lepidic growth pattern, most commonly papillary, micropapillary, acinar, solid or mucinous, and the appearance of foci of stromal invasion [109, 110].

Both lesions are most commonly non-mucinous adenocarcinomas, and mucinous AIS and MIS are extremely rare.

On chest CT, both non-mucinous AIS and MIA appear as ground glass nodules (GGN) [110]. The diagnosis of AIS and MIA is not possible on the basis of tissue biopsy or cytology, and requires microscopic evaluation of an entire surgically resected lesion. Needle biopsy or intraoperative examination of GGN to establish the diagnosis are not recommended. Both types of lesion carry a very favourable prognosis, with 100% of the patients surviving 5 years after radical surgery [109, 110].

The most recent, eighth edition of the TNM classification of lung cancer (2016) introduced a new principle of pathological evaluation of tumour size (pT) for tumours with part-solid appearance on CT (part-solid non-mucinous adenocarcinoma). Apart from total tumour diameter, it is now essential to determine the size of the solid component of the tumour, which corresponds to the actual invasive component. Reporting the both sizes is therefore recommended, although only the pT category is affected by the invasive component [111].

Invasive adenocarcinoma is defined as a tumour with morphological structures suggestive of glandular pattern of differentiation on standard (H&E) microscopic examination (tubular, papillary or micropapillary structures) or with mucin in the tumour cells on histochemical examination, or with the expression of immunohistochemical markers of glandular differentiation (TTF-1, napsin A, CK7) [109]. Adenocarcinomas are an extremely heterogeneous group of tumours in terms of morphology and genetics [112, 113]. The number of mutations identified in lung adenocarcinomas are very large, and new mutations are constantly being discovered. However, targeted therapies are only available for some of them. The most common mutations are *EGFR*, *KRAS*, *BRAF* and *NRAF* mutations and *ALK*, *ROS1* and *MET* rearrangements [109, 114, 115]. The morphology of adenocarcinoma does not only indicate its degree of differentiation but also allows to predict the possibility of mutations, mainly *EGFR*, *ALK* and *KRAS* mutations [113, 115, 116].

Lepidic carcinomas are well-differentiated tumours with favourable prognosis and often

show *EGFR* mutations. *EGFR* mutations are often seen in acinar, papillary and micropapillary carcinomas. Solid tumours with a component of signet ring differentiation and acinar tumours with cribriform structures may show *ALK* rearrangements, while mucinous tumours may display *KRAS* mutations [113, 116]. In view of the above, the histopathological diagnosis of invasive adenocarcinoma of the lung requires specification of the predominant morphological pattern and the proportions of the remaining microscopic components, especially those that indicate a more aggressive course of the disease (solid and micropapillary components) [109].

13. Additional programmes accompanying lung cancer screening

In 2010, the WHO published guidelines on cancer screening methodology. The document stated that the four most common causes of death in the modern world are cardiovascular disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and cancer. All these conditions have the same risk factors and, given the fact that all four are preventable, it is recommended that, if possible, screening covering all these illnesses should be provided together [117]. Low-dose computed tomography offers the possibility to assess the severity of coronary artery calcification on the scan images, i.e. the CAC score, and the severity of emphysema using a dedicated software. Performing spirometry in the participants of the screening programme will enable the diagnosis of COPD.

The assessment of the coronary artery calcium (CAC) score or the severity of coronary artery calcification is feasible on LDCT, and has been demonstrated to be non-inferior to contrast-enhanced CT with ECG gating in assessing the risk of death and coronary events. The presence of calcifications directly points to the presence of subclinical coronary artery disease in the individual, and the intensity of calcifications corresponds to the severity of the process. The CAC score assessment was included in the ACC/AHA guidelines in 2010, and in the European Society of Cardiology guidelines in 2012, as Class IIa recommendation (designation as a useful and valuable method). The CAC score can easily be assessed and measured in each LDCT performed in screening programmes, which is currently recommended in countries where such programmes are in place. The CAC score is considered a valuable cardiovascular risk marker in asymptomatic adults over the age of 40 [118–120].

Emphysema and COPD are known positive predictors of lung cancer risk, affecting not only lung cancer incidence but also all-cause mortality. Epidemiological studies, including lung cancer screening programmes, have demonstrated a 2- to 4-fold increase in new cases of lung cancer in patients with COPD compared to healthy individuals. This risk is partially due to emphysema susceptible for qualitative or semi-quantitative evaluation on LDCT scans. Emphysema is a stand-alone risk factor of lung cancer also in non-smokers. Risk scales have been developed for COPD patients to identify individuals at an increased risk of developing lung cancer, which considerably increases the effectiveness of screening programmes, while reducing the side effects. Patients with COPD should be included in lung cancer screening programmes. Additionally, the detection of COPD in patients unaware of having this condition, will allow them to receive the preventive and therapeutic intervention in the form of a smoking cessation programme and appropriate treatment [121].

The additional performance of simple and inexpensive tests in the participants of the lung cancer screening programme, such as a standardised measurement of blood pressure, cholesterol and HbA1c (glycated haemoglobin), will allow the detection of undiagnosed conditions in a large proportion of these individuals, and in order to provide them with appropriate treatment, adjust treatment in those inadequately managed.

14. Quality evaluation and training/education. Registration and certification of the centres

A Centre for Early Lung Cancer Detection Studies (CELCDS) should be a centre that meets the quality requirements specified in the operating guidelines prepared by Scientific Societies and/or by the Ministry of Health published in the future as the official announcement. The CELCDS should operate in centres with a high level of competency and be closely associated with the strategy for the diagnosis and treatment of lung cancer prepared by the Ministry of Health.

- A. The activities of the centres are subject to **total quality management** (TQM) with the use of effectiveness (quality) indicators specified by Scientific Societies and/or the Minister of Health.
- B. For the purposes of the reporting and monitoring of the diagnostic and therapeutic processes and their outcomes, the **Screening Registry** is created to include all the evaluated and treated patients.

- C. The CELCDS follows the **operating guidelines** (published in the future as the official announcement of the Minister of Health), which are subject to monitoring and quality assessment (peer review, benchmark etc.).
- D. The CELCDS reports the completed activities and the key results of the studies, which is necessary for reconciliation of the services and for monitoring of the quality and effectiveness, and for research purposes. The **Lung Cancer Registry** is created from the reported data.
- E. Early lung cancer detection studies are subject to a pilot study (e.g. 3 to 5 centres), which will allow the detailed conditions for commissioning these centres on the national scale, to be defined.
- F. The CELCDS reports the completed activities and the key results of the studies, which is necessary for reconciliation of the services and for monitoring of the quality and effectiveness, and for research purposes. The **Screening Registry** is created from the reported data.
- G. New CELCDS was created basing on training at the existing centres of competence identified in the pilot programme after obtaining accreditation from the Ministry of Health.

15. Involvement of thoracic surgeons in preparation of screening programmes

Surgeons should be engaged in the screening programme and play an important role in its preparation and implementation. Thoracic surgeons perform a major function within the multidisciplinary tumour board and his/her decisions must be in conformity with current recommendations concerning diagnosis and treatment of early non-small cell lung cancer detected in the screening. The main goal is to participate actively in the diagnostic workup and decision making to eliminate or minimise surgery for benign conditions. The extent of surgery for benign lesions during CT screening should be monitored and reported as an indication of surgical quality. Moreover, important surgeons' tasks in the screening team are the following: optimisation of the management of screen detected nodule, reduction of false positive rates of surgical biopsies and decline of surgery related trauma.

A thoracic surgeon participating in the screening programme, should fulfil the requirements and qualifications described in the „Recommendations from the European Society of Thoracic Surgeons (ESTS) regarding computed

tomography screening for lung cancer in Europe” prepared and published in European Journal of Cardio-Thoracic Surgery by the group of ESTS experts [31]. We recommend to strictly follow these recommendations in the preparation and implementation of lung cancer screening programme in appointed centres.

Conflict of interest

Witold Rzyman and Mariusz Adamek developed the concept and design of the Consensus statement on a screening programme for the detection of early lung cancer in Poland.

All of the authors contributed equally to developing the Consensus statement on a screening programme for the detection of early lung cancer in Poland.

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