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Review article

Low-dose computed tomography screening reduces lung cancer mortality

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ABSTRACT

Lung cancer causes an estimated 1.6 million deaths each year, being the leading cause of cancer-related deaths in the world. Late diagnosis and, in some cases, the high aggressiveness of the tumour result in low overall five-year survival rates of 12% among men and 7% among women. The cure is most likely in early-stage disease. The poor outcomes of treatment in lung cancer resulting from the fact that most cases are diagnosed in the advanced stage of the disease justify the implementation of an optimal lung cancer prevention in the form of smoking cessation and screening programmes that would offer a chance to detect early stages of the disease, while fitting within specific economic constraints. The National Lung Screening Trial (NLST) – the largest and most expensive randomised, clinical trial in the USA demonstrated a 20% mortality rate reduction in patients who had undergone chest low-dose computed tomography (LDCT) screening, as compared to patients screened with a conventional chest X-ray. Results of the NLST enabled the implementation of lung cancer screening programme among highrisk patients in the USA and parts of China. In 2017, recommendations of the European Society of Thoracic Surgeons also strongly recommend an implementation of a screening programme in the EU. Further studies of improved lung cancer risk assessment scores and of effective molecular markers should intensify in order to reduce all potential harms to the high-risk group and to increase cost-effectiveness of the screening.

Contents

1. Introduction

Lung cancer causes an estimated 1.6 million deaths each year, being the leading cause of cancer-related deaths in the world [1,2]. It accounts for 20% and 9% of new cases of cancer in males and females, respectively [3]. Late diagnosis and, in some cases, the high aggressiveness of the tumour result in low overall 5-year survival rates of 12% among men and 7% among women [3]. Lung cancer mortality equals the combined mortality in the next four most common cancers. In 2015, it caused almost 18% of deaths worldwide and 20% of deaths in the European Union (EU). The incidence and mortality rates in Poland are among the highest in

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the EU [3]. Lung cancer is responsible for over 30% and 15% of cancer deaths in Polish men and women, respectively, accounting for over 22,000 deaths per year [3].

Five-year survival rates decrease with increasing disease stage. In stages I, II, III and IV, the rates are 60–80%, 20–30%, 16% and less than 10%, respectively [4]. Surgery is the most effective treatment with curative intent. The cure is most likely in early-stage disease. Hamatake et al. demonstrated 3- and 5-year survival rates of 95% and 92%, respectively, in patients with peripheral lung tumours of less than 1 cm in diameter following lobectomy and mediastinal lymphadenectomy [5]. Unfortunately, in the majority of thoracic surgical centres worldwide, the proportion of patients treated for stage I disease does not exceed 50%.

2. Review

2.1. Historical background

The poor outcomes of treatment in lung cancer resulting from the fact that most cases are diagnosed in the advanced stage of the disease justify the implementation of an optimal lung cancer screening programme that would enable early detection of the tumour, while fitting within specific economic constraints.

The effectiveness of various lung cancer screening programmes in high-risk patients has been assessed in multiple studies in the last decade. Some of these programmes were based on chest radiography (CXR), while others on low-dose computed tomography (LDCT) [6,7]. Two large clinical trials have shaped the current view on lung cancer screening.

The non-randomised International Early Lung Cancer Action Program (I-ELCAP) published in 2006 showed that it was possible to detect early stage IA lung cancer using LDCT with a predicted 10-year survival rate of 88% [8,9]. The study enrolled over 31,000 smokers, including former and passive smokers, aged 40 to 90 years. Nodular changes were detected in 30% of the participants and lung cancer in 2–3%.

The randomised National Lung Screening Trial (NLST) conducted in the United States in 2012 enrolled over 54,000 persons at high risk of developing lung cancer. Eligibility criteria included age 55 to 74 years and a significant cumulative exposure to tobacco smoke. The study compared the effectiveness of LDCT with that of CXR in reducing lung cancer mortality. Participants were randomised to two screening arms and underwent either CXR screening or LDCT screening annually for three consecutive years. Detection rates for stage I, II, III and IV lung cancer were, respectively, 50%, 7%, 21% and 22% in the LDCT arm and, respectively, 31%, 8%, 25% and 36% in the CXR arm. LDCT screening, compared to CXR screening, allowed to detect more lower-stage lung cancers and to perform fewer pneumonectomy procedures (1% in the screening study vs 10% in symptomatic patients) [10]. Most importantly, however, the NLST demonstrated a mortality rate reduction of 20% in patients who had undergone LDCT screening [11,12]. The detection rate of LDCT-diagnosed lung cancer reached 2.4% over a period of three years, and the positive and negative predictive values of LDCT were, respectively, 1.2% and 100% [12].

The 20-percent reduction in mortality rate demonstrated in the NLST became a major supporting argument in the debate on the effectiveness of LDCT screening and its implementation into everyday clinical practice [11,13–18]. Results of the NLST enabled the implementation of lung cancer screening programme among high-risk patients in the USA and parts of China (18). The United States Preventive Services Task Force (USPSTF) recommends such screening in people aged over 55 years with a smoking history of at least 30 pack-years [19]. Since 2014, the cost of the programme has been covered by the Center for Medicare and Medicaid Services.

2.2. Current views on lung cancer screening

Currently, two studies – the Dutch-Belgian NELSON study and the United Kingdom Lung Cancer Screening (UKLCST) Trial are being conducted in Europe. The NELSON study has enrolled nearly 16,000 thousand people aged 50 to 75 years with a smoking history exceeding 15 pack-years in the Netherlands and Belgium. There are two screening arms in the study: the LDCT screening arm and the observation arm. It has been estimated that the mortality rate should be reduced by 25% in a 10-year-long follow-up period [20,21]. The results were expected in 2017 and are particularly awaited in the European countries. In addition to the NELSON and UKLCST studies, a few other randomised and non-randomised pilot lung cancer screening programmes have been performed in Italy, Germany, United Kingdom, Denmark and Poland [19,22–24]. It is, however, unlikely that the statistical power of all these studies, even if pooled analysis is performed, will be comparable to that of the NLST [25]. To some extent disparity between the European studies and the NLST results from the differences of histological subtypes of a diagnosed lung cancer both in the USA and Europe. By the time of publication of the NLST results the main subtype of lung cancer diagnosed in the USA was adenocarcinoma, while in Central Europe, for example in Poland, it was squamous cell carcinoma. As indicated by the Polish Lung Cancer Registry data, in 2013, adenocarcinoma became the main histological subtype of lung cancer resected in Poland [26]. So far, the activity of the European countries has been limited to the release of joint recommendations by the European Radiological Society and the European Respiratory Society, statements by the Swiss University Hospitals and by the European Society of Medical Oncology, and, most recently, recommendations by the European Society of Thoracic Surgeons and by the Nordic countries expert group [27–31]. It has been advised to implement lung cancer screening for populations at high risk of lung cancer as part of long-term programmes which should be carried out at well-equipped, multidisciplinary and certified clinical centres [25]. Recently published “European position statement on lung cancer screening” recommends implementation of LDCT screening throughout Europe as soon as possible [32].

According to the NCCN guidelines, fine-needle aspiration biopsy should be considered in cases of high suspicion of tumour malignancy, as it is a well-established diagnostic tool [33,34]. In selected cases, other methods such as endobronchial ultrasound (EBUS) or electromagnetic navigation are available in centres of excellence in thoracic oncology. Based on the NCCN guidelines, the criteria for suspicion of malignancy are: hypermetabolism higher than the background of the surrounding lung parenchyma regardless of the absolute standard uptake value (SUV) [33]. However, evaluation of the suspicion requires a multidisciplinary approach with the expertise of thoracic radiologists, chest physicians and thoracic surgeons [33,34]. Transthoracic fine-needle aspiration biopsy is an efficient and well-documented tool to establish a cytological diagnosis in these tumours [34].

Studies of circulating molecular biomarkers of lung cancer are currently underway [28,29]. Identification of such markers would make it possible to preselect groups of patients at increased risk of lung cancer eligible for LDCT screening [28,29,35]. Several molecular signatures differentiating early-stage lung cancer individuals from the rest of the population have already been identified in serum and plasma, but these findings require further validation [29,35,36].

2.3. Diagnosis and treatment

Chest LDCT is a safe non-contrast diagnostic procedure involving 10–30% lower radiation doses that does the standard

CT examination. The dose absorbed by the individual is 2 mSv (37). The purpose of the scan is to detect non-calcified nodules suspicious for lung malignancy based on their morphology and size. The high sensitivity of this method is associated with the potential for detection of small-sized nodules [35,36]. Unfortunately, lung cancer screening based on LDCT is also associated with a high rate of false positive results. The positive predictive value (PPV) of an incorrect result of LDCT screening for lung cancer is merely 1.7% for nodules measuring 7 to 10 mm, but as much as 11.9%, 29.7% and 41.3% for nodules measuring 11 to 20 mm, 21 to 30 mm and more than 30 mm, respectively [38].

The NLST achieved a sensitivity and specificity of 93.8% and 73.4%, respectively, in the LDCT arm (versus 73.5% and 93.1%, respectively, in the CXR arm) with a PPV of 3.8% for nodules measuring 4 mm or more [39]. The study reported a total of 24.2% of positive results, 96.4% of which were false positive [39]. The majority of the positive cases underwent additional radiologic examination, but about 2.5% of them required invasive diagnostics such as flexible bronchoscopy, fine-needle biopsy and resection by video-assisted thoracoscopic surgery [39].

The protocols of three major clinical trials (i.e. I-ELCAP, NLST and NELSON) differ quite significantly. Apart from the already discussed NLST, the two other trials define a positive result as a diagnosis of a nodule measuring more than 5 mm [8] or either more than 10 mm or 5 to 10 mm along with a 25% increase in size in less than a year on CT [11]. As a consequence, the proportion of positive results dropped from 27% in the NLST to 2.7% in the NELSON study. In addition, the NELSON based its pulmonary nodule management on volumetric analysis [40,41]. For solid and part-solid nodules, screening is considered positive if volume is greater than 500 mm^3 or volume-doubling time (VDT) is lower than 400 days [42]. For non-solid nodules, screening is considered positive if VDT is lower than 400 days [42]. This is the first randomised lung cancer screening trial to have implemented such an approach and led to a significant drop of false positive results (2.7%) [40,41]. Rolfo et al. concludes that semi-automated volumetric analysis in the NELSON study is an accurate and precise method for analysing the growth rate of solid nodules [43]. However, it requires a further, comprehensive assessment and the support of radiologist experience [43]. Such discrepancies between the American and the European studies indicate a lack of consensus regarding the optimal diagnostic protocol for the detected lesions in the lung parenchyma. However, the recently published "European position statement on lung cancer screening" recommends semi-automated volume and VDT measurement of detected solid nodules, while non-calcified baseline lung nodules greater than 300 mm^3 and new lung nodules greater than 200 mm^3 should be managed by multidisciplinary teams [32].

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 (NCCN) guidelines, nodule assignment should be based on the guidelines of the American College of Radiology Lung-RADS [33,44]. The management in each of the category is based on the nodule size.

Solid nodules

1. Nodules <6 mm require observation and a repeat LDCT after 12 months until the risk of malignancy is excluded.
2. Nodules 6 to <8 mm require a repeat LDCT after 6 months.
3. Nodules 8 to <15 mm 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 [33].
4. Nodules ≥15 mm require a chest CT with contrast and/or a PET-CT.
5. 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 a PET-CT should be managed as follows:

1. Low risk of lung cancer: LDCT in 3 months.
2. High risk of lung cancer: Fine-needle biopsy with aspiration of an adequate amount of material for histological and molecular examination or surgical resection of the nodule should be performed [37,39]. Where the biopsy reveals no malignancy, the patient should undergo LDCT after 12 months of observation.

Part-solid nodules

1. Nodules <6 mm require observation and a repeat LDCT after 12 months until the risk of malignancy is excluded.
2. Nodules ≥6 mm or nodules <6 mm with a solid component require a repeat LDCT after 6 months.
3. Nodules ≥6 mm or nodules 6 to <8 mm with a solid component require a repeat LDCT after 3 months or a consideration of PET-CT.
4. Nodules ≥8 mm with a solid component require a chest CT with contrast and/or a PET-CT.

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

1. Low risk of lung cancer: LDCT in 3 months.
2. High risk of lung cancer: Fine-needle biopsy with aspiration of an adequate amount of material for histological and molecular examination or surgical resection of the nodule should be performed [33,44,45]. Where the biopsy rules out malignancy, the patient should undergo LDCT after 12 months of observation.

Non-solid nodules

1. Nodules <20 mm require observation and LDCT after 12 months until the risk of malignancy is excluded
2. Nodules >20 mm require a repeat LDCT after 6 months.

Non-solid nodules are mainly adenocarcinomas in situ (AIS) or minimally invasive adenocarcinomas (MIA) – formerly known as bronchioalveolar carcinomas (BAC) [46]. Provided these nodules are completely resected, various studies report a 5-year disease-free survival of 100% [45,47–52]. Since non-solid nodules may be partially benign, data suggest that such incidental findings on CT scans will resolve and many of them may not progress to invasive cancer [9,38,53]. In comparison, solid and part-solid nodules are more aggressive and grow faster – what should be considered in the assessment and follow-up evaluation [46,48,54,55].

In addition, any new nodule detected in a patient already under observation is considered a malignant change.

In contrary to the U.S. follow-up models, in Europe the volumetry of the nodules used as a tool to determinate their potential malignancy has gained much more recognition. It is mainly due to an extensive work-up of this tool in the NELSON study, in which 6% of the participants screened had a positive result and 2.6% were diagnosed with lung cancer. Thus, Horeweg et al. showed that a concise, volumetry-based screening strategy may result in both few positive and false positive (1.2%) results, whereas also in a respectively high PPV of 40.6% [42]. It seems that

volumetry will play an important role in the European guidelines that are underway.

2.4. Additional findings

It should be emphasised that the studies conducted so far have demonstrated that LDCT enables an effective detection of small pulmonary nodules. This imaging modality does not, however, detect any additional abnormalities that can be detected by contrast-enhanced chest CT. The limitations of LDCT should be taken into account in the context of clinical and legal consequences of false negative results related to any missed extraparenchymal pathologies. Such additional findings are described as any abnormal findings located in the mediastinum, bronchi, lung parenchyma, blood vessels or any upper abdominal structures visualised by LDCT. Any such finding, whatever its type or form, must be properly described in the LDCT report [56]. The contribution of such information to the value of the radiological examination is unknown and depends on the further course of treatment [57,58]. For example, data from the NELSON study and the NLST indicate a low clinical usefulness of such additional findings (8% and 10% of diagnostically useful findings, respectively) [11,59].

Several cohort studies have shown a 2- to 4-fold increase in the risk of lung cancer among patients with chronic obstructive pulmonary disease (COPD) [60–63]. It has also been demonstrated that inclusion of such patients in LDCT screening programmes would increase the effectiveness of these programmes and could reduce mortality in COPD patients [64]. Also, there are two other important groups which could be included in the screening programmes: patients with a family history of lung cancer and patients with emphysema. Other subsets of patients that should be taken into consideration are: patients with asbestos exposure, inhabitants of regions with contaminated water and persons working with chemical substances such as oils, paints, coal, or welders.

LDCT enables a limited evaluation of the following:

1. development of COPD, emphysema, interstitial lung disease, and mediastinal pathologies,
2. coronary artery calcification (CAC) score [65],
3. radiological breast examination based on the Breast Imaging Reporting and Data System (BI-RADS) [56],
4. osteoporosis.

2.5. Other issues

Lung cancer screening programmes are useful in the promotion of smoking cessation [66–68]. Cessation rate in the NELSON study reached 16% versus 6% in the general population [59,69]. Aalst et al. reported that all the NELSON study participants were eager to stop smoking more than average [68]. Other trials have also shown the efficacy of smoking cessation at yearly LDCT examinations [66]. Pastorino et al. concluded that stopping smoking reduces the overall mortality among LDCT screening programmes' participants and its beneficial effect is threefold to fivefold greater than the one achieved by earlier detection in NLST [70]. Such occasions of being actively involved in the screening programme and CT scanning are "teachable moments" to improve smoking behaviour [23,56,68,69,71]. Pyenson et al. proved that introduction of a formal, strict smoking cessation protocol along with the lung cancer screening may significantly increase the overall cost-effectiveness of the programme, as the economic aspect seems to be directly related to the benefits derived from smoking cessation [58].

While lung cancer screening does reduce lung cancer related mortality, it has a low impact on the detection of malignant tumours itself [11,72–74]. This is due to the fact that many small nodules of less than 2 mm in diameter are detected on LDCT and it is very difficult to determine whether they are malignant or benign. This leads to many false positive results, which decreases the specificity and PPV on the one hand and expose the patients to unnecessary and expensive diagnostic procedures on the other [14,75]. For this reason, the minimum size of the nodule requiring intensified LDCT follow-up is being gradually increased. It is estimated that a significant share of invasive diagnostic procedures are performed in patients with benign pulmonary nodules. Given the fact that all screening procedures are offered to healthy, asymptomatic people, the exposure of such individuals to any invasive diagnostic procedure should be considered a last resort [76].

Screening programme coordinators should be aware of the risks and unintended consequences of any unnecessary treatment of additional findings, such as the high cost of additional evaluation, its complications and the patient's anxiety [57]. Therefore, contemporary screening programmes place particular emphasis on a thorough assessment of risk factors, implementation of risk prediction models and the use of advanced radiological diagnostic equipment and procedures [76]. In comparison to mammography in breast cancer screening or faecal occult blood testing in colorectal cancer screening, the potential of LDCT as a screening tool is greater. In the NLST, the number of participants needed to be screened to save one life was 320. In contrast, breast and colorectal cancer screening programmes require over 780 and 1250 participants to be screened, respectively [77]. Based on these figures, LDCT screening proves more efficient than the other screening programmes already widely implemented worldwide [78]. The drawback of LDCT is its high cost as a diagnostic tool. A CT scan is much more expensive than a mammogram or a faecal occult blood test. And yet, more recent studies prove that lung cancer screening programme is cost-effective. Pyenson et al. demonstrated that inclusion of optimal smoking cessation protocol could significantly reduce cost-effectiveness [58]. Ten Haaf et al. simulated various clinical scenarios and calculated net discounted costs and life-years gained in the Canadian population. For example, if the inclusion criteria were current and former smokers (who quit less than 10 years ago) aged 55–75, who smoked more than 40 pack-years, the incremental cost-effectiveness ratio (ICER) would be 41,136 Canadian dollars [79]. Assuming that Canadian healthcare system accepts the cost-effectiveness threshold of 50,000 Canadian dollars per life-year gained, such a scenario proves the cost-effectiveness of the lung cancer screening programme [79]. Simulations of cost-effectiveness should, however, be region-specific and no such calculations have been performed for Central Europe so far.

The issue of the appropriate positioning of the lung cancer screening programme is commonly raised. In the NLST, despite the fact that the patient management protocol was prepared by the investigators, 82% of the sites were large, academic medical centres [80]. Similarly, the current guidelines of the International Association for the Study of Lung Cancer, NCCN, USPSTF, Medicare, American Lung Association, American Association for Thoracic Surgery and American Cancer Society state that lung cancer screening programmes should be organised in such large hospitals [33,81,82]. The multidisciplinary team should include chest physicians, pathologists, radiologists, thoracic surgeons and oncologists [31]. Some technical requirements concerning the quality of CT examination should also be fulfilled [31]. The impact of the setting details may be important, but on the other hand current lung cancer screening programme in the USA is held widely, also being based in local community hospitals [14]. As the

thoracic oncology is a relatively narrow medical discipline, the key aspect is who will be interpreting the data rather than where will they be implemented. The main issue in the future will be to find an accurate molecular or radiomic signature of lung cancer and such studies are currently underway. Some of these studies are phase IV studies, i.e. involve validation in prospective screening cohorts (autoantibody, miRNA and RNA signature from bronchial brushing) [83–85].

Another important issue is overdiagnosis, which refers to detection of subclinical changes or indolent tumours that would not decrease the patient's life expectancy. Detection of such changes usually leads to unnecessary diagnostic procedures and treatment, anxiety and negative economic effects. On the other hand, overdiagnosis overestimates curability and survival rates. In the NLST, over 18% of all the detected nodules were indolent [86].

The available literature has also pointed to the psychological aspect of participation in lung cancer screening programmes. Patient exposure to in-depth examination or unnecessary invasive diagnostic procedures may cause anxiety, which is directly linked to the perspective of a potential lung cancer development [57]. A negative psychosocial aspect is also described among people who do not accept the idea of living with small pulmonary nodules in their bodies. Nonetheless, the impact of LDCT screening on the quality of life is unclear. In the NLST, no increased rate of anxiety or any differences in the quality of life were observed at 1 and 6 months after the end of the trial [87]. Similarly, 88–99% of the NELSON study participants did not reveal any negative psychological effects of participating in the screening. Even though 46% of the participants did report a feeling of stress associated with waiting for the results of the radiological examination, no differences in the quality of life were observed 2 years later [88].

The advances in computed tomography have enabled the acquisition of diagnostic images at the smallest possible effective radiation dose of 1.3 mSv in women and 1.0 mSv in men in the case of LDCT. Based on the NLST, it has been estimated that the cumulative radiation dose absorbed during 3 years of lung cancer screening is about 8 mSv (including screening scans and diagnostic scans). Nonetheless, LDCT still carries the risk of radiation-induced lung cancer, a risk that is twice as high in smokers than in the general population. The risk of radiation-induced lung cancer in LDCT-screened patients is 0.02% and 0.05% in male and female populations, respectively, with no correlation between the age of joining the screening programme and the risk of developing radiation-induced lung cancer.

3. Conclusions

Despite recent scientific advances, lung cancer remains the most common cancer-related cause of death in the world [1,2]. Late diagnosis is responsible for the fact that the curability rate has not increased significantly since the 1960s. In addition, the mortality rate is estimated to increase by 86%, to over 3 million per year in 2035 [24]. The implementation of lung cancer screening and smoking cessation programmes in high-risk group offers a chance to reduce the mortality rate [25]. The diagnostic accuracy of screening may be potentially increased by improving the selection criteria and/or adding other early detection tools, such as radiomics or molecular testing [28]. Trials looking into these possibilities are well underway in the United States, United Kingdom, Poland and Italy [89]. This would enable to better select patients at a significantly higher risk of lung cancer and, in patients with detected nodules on LDCT, to differentiate benign from malignant tumours detected on CT. Detection of markers in body fluids seems very promising but requires further studies [29,35,90,91].

Conflict of interest

The authors declare no conflict of interests.

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