Advances in Medical Sciences 63 (2018) 230–236

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Review article

Low-dose computed tomography screening reduces lung cancer mortality

Marcin Ostrowski*, Tomasz Marjański, Witold Rzyman

Department of Thoracic Surgery, Medical University of Gdańsk, Gdańsk, Poland

ARTICLE INFO

Article history:
Received 26 July 2017
Accepted 17 December 2017
Available online xxx

Keywords:
Lung cancer
Screening
Low-dose computed tomography

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.

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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

* Corresponding author at: Department of Thoracic Surgery, Medical University of Gdansk, Smoluchowskiego 17, 80–214 Gdansk, Poland. Tel.: +48 58 349 3130; fax: +48 58 349 3140.
E-mail address: m.ostrowski@gumed.edu.pl (M. Ostrowski).

https://doi.org/10.1016/j.advms.2017.12.002
1896-1126/

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 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].