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MINIREVIEWS

Screening for lung cancer with chest computerized tomography: Is it cost efficient?

Tomasz Jarosław Szczęsny, Małgorzata Kanarkiewicz, Janusz Kowalewski

Tomasz Jarosław Szczęsny, Janusz Kowalewski, Department of Thoracic Surgery and Tumors, Oncology Center in Bydgoszcz, 85-796 Bydgoszcz, Poland

Małgorzata Kanarkiewicz, Department of Pharmaceutical Technology, Nicolaus Copernicus University Collegium Medicum in Bydgoszcz, 85-796 Bydgoszcz, Poland

Janusz Kowalewski, Department of Thoracic Surgery and Neoplasms, Medical Faculty in Bydgoszcz, Nicolaus Copernicus University in Toruń, 85-796 Bydgoszcz, Poland

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Correspondence to: Tomasz Jarosław Szczęsny, MD, PhD, Department of Thoracic Surgery and Tumors, Oncology Center in Bydgoszcz, Romanowskiej Str. 2, 85-796 Bydgoszcz, Poland. szczesny@lungcancer.med.pl
Telephone: + 48-52-3743574
Fax: +48-52-3743436

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Abstract

Despite lung cancer (LC) screening by low-dose computerized tomography (LDCT) gaining many proponents worldwide, for many years it was not recognized as a life-prolonging and cost-effective procedure, until recently. Prospective observational studies had not been able to prove that this screening prolongs survival, but they helped to specify the inclusion and exclusion criteria. Long-awaited results of a prospective, randomized trial finally provided the evidence that LC screening with LDCT can prolong survival of the screened population. Several cost-effectiveness analyses were performed to justify mass introduction of this screening. Results of these analyses are equivocal, although conclusions highly depend upon inclusion and exclusion criteria, methods of analysis and prices of medical procedures which differ between countries as well as the incidence of other pulmonary nodules, especially tuberculosis. Therefore, cost-effectiveness analysis should be performed separately for every country. Cost-effectiveness depends especially upon the rate of false-positive results and the rate of unnecessary diagnostic, screening and treatment procedures. To ensure high cost-effectiveness, LC screening should be performed in accordance with screening protocol, in dedicated screening centers equipped with nodule volume change analysis, or as a prospective non-randomized trial, to ensure compliance with the inclusion and exclusion criteria. To ensure high cost-effectiveness of LC screening, future research should concentrate on determination of high-risk groups and further specifying the inclusion and exclusion criteria.

Key words: Lung cancer; Non-small cell lung cancers; Screening; Cost-effectiveness; Computerized tomography; Low-dose computerized tomography

Core tip: Results of prospective, randomized trial finally provided the evidence that lung cancer screening with computerized tomography prolongs survival of the screened population. Several cost-effectiveness analyses were performed to justify mass introduction of this screening, but their results differ between countries. Cost-effectiveness depends especially upon the rate of false-positive results which increase the number of unnecessary medical procedures. Therefore, to ensure high cost-effectiveness, lung cancer screening should be performed in accordance with screening protocol, in dedicated screening centers equipped with nodule volume change analysis, or as a prospective non-randomized trial, to ensure compliance with the inclusion and exclusion criteria.

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INTRODUCTION

Computerized tomography is today widely available in most, even moderately developed, countries. When used for screening of lung cancer (LC), it allows to detect neoplasm which is the leading cause of cancer death[1] in an early stage, which dramatically improves cure rate of newly diagnosed LC from 12%[2] to over 80%[3]. Despite that, the only country where LC screening with low-dose computerized tomography (LDCT) is widely used is Japan, where such programs are officially supported since 30 years ago. The main reasons why computerized tomography (CT) screening has not become popular worldwide are, developed in the United States, the principles of Good Clinical Practice (GCP) and Evidence-Based Medicine (EBM), which require new diagnostic and therapeutic methods to be well tolerated and to improve survival of the group in which they are administered, and finally, to confirm this in a prospective, randomized trial[4].

These rules of GCP and EBM are a cornerstone of modern medical science and do well in the implementation of new therapeutic procedures and medicines, but their administration to new screening procedures is controversial, for several reasons. Firstly, it is not clear what poor toleration of a screening procedure means: can it be, *e.g.,* discomfort caused by detection of a benign nodule? Also, performing prospective randomized trial on a screening procedure never assesses a new method of screening, but always compares two methods of screening of different intensity, because it is believed unethical not to administer any screening in the control arm. An exception is an ongoing in Holland, Belgium and Denmark NELSON trial, in which control arm receives only community care[5]. Moreover, participants often change arms of trial arbitrarily. Finally, since the primarily criterion of the effectiveness of cancer treatment is a 5-year survival, to assess the impact of screening on the survival of the study population, at least one generation should be sacrificed. Meeting the requirements for obtaining recommendation for new screening procedures is so difficult that several consecutive international randomized trials assessing the value of mammography in detecting breast cancer showed no effect on survival of the study population[6]. Fortunately for breast cancer patients, despite lack of proven impact on survival, mammography programs were not discontinued and subsequent randomized trials provided expected evidence[7].

From this perspective, LC patients are less lucky than breast cancer patients. Despite early detected LC having a higher cure rate than breast cancer of similar size, and a 5-year survival almost inevitably meaning cure (unlike in breast cancer which can recur more than 20 years after radical treatment), despite it being inappropriate to call LC a "deserved" disease (most new cases develop in patients who never smoked cigarettes or stopped smoking over 10 years ago[8]), programs for LC screening in most countries are still waiting for official support and recommendations.

Due to reasons mentioned above, waiting for results of a prospective randomized trial on chest LDCT screening performed in the United States[9] did not satisfy supporters of this screening. They have organized, mostly in the United States, non-randomized observational studies[10], to show that LDCT is able to increase resectability rate, cure rate and prolong survival in the screened population[3]. Finally, the National Lung Screening Trial provided evidence of a 20% reduction in lung cancer mortality and a 6.7% decrease in all-cause mortality among current and former smokers at high risk[11]. As a result, the United States Preventive Services Task Force (USPSTF) has recommended this screening, allowing coverage of LDCT to private health insurers under provisions of the Affordable Care Act which states that LDCT must be covered without cost-sharing by qualified health plans starting January 1, 2015. Because private insurers cover medical expenses mostly for population below 64 years, while 70% of new lung cancer cases are diagnosed above that age, the decision of Centers for Medicare and Medicaid Services which provides medical insurance for elderly population, will be of key importance[12]. Following USPSTF recommendations, appropriate recommendations have been adopted by other organizations with an interest in LC, including the National Comprehensive Cancer Network, American Association for Thoracic Surgery, American College of Radiology, Society of Thoracic Surgeons, International

Table 1 Results of baseline screening with low-dose chest computerized tomography in asymptomatic smokers

Institution, country	Number of participants	Number (%) of positive results	Number (%) of diagnosed lung cancer	NSCLC	Stage I disease	Mean age of participants
Early Lung Cancer Action Project (ELCAP), United States[10,14]	1000	233 (23)	27 (2.7)	96%	85%	67
New York Early Lung Cancer Action Project (NY-ELCAP), United States[15]	6295	906 (14)	101 (1.6)	94%	97%	66
International Early Lung Cancer Action Project (I-ELCAP), United States[3]	31567	4186 (13)	405 (1.3)	-	86%	61
Mayo Clinic, United States[9,16,17]	1520	782 (51)	30 (2)	93%	75%	59
Anti-Lung Cancer Association (ALCA), Japan[18]	1611	186 (11.5)	13 (0.9)	100%	77%	60
University of Munster, Germany[19,20]	817	350 (43)	11 (1.3)	91%	70%	53
Pomeranian Pilot Program of Lung Cancer Screening, Poland[21]	2002	982 (49)	11 (0.5)	100%	91%	59
Total	44812	7625 (17)	598 (1.3)			
Median	6402	1089 (17)	85 (1.3)			

NSCLC: Non-small cell lung cancers.

Association for the Study of Lung Cancer, American College of Chest Physicians, and the American Cancer Society[13].

DISCUSSION

Lung cancer is diagnosed in about one out of 75 LDCT baseline examinations, as shown in the results of studies presented in Table 1.

In Table 1 only results of single baseline screenings for LC are presented. The age of participants varied between studies, in a Japanese study patients accrued were 40-79 years old, but most studies did not include patients below 50 years old. Screening was addressed to persons who had smoked at least 10 pack-years of cigarettes, but in a Japanese study 16% of patients did not have smoking history[18]. The rate of pulmonary lesions also varies. On average, in one out of 6 examinations pulmonary lesions are found, but they are more common in populations which had a common contact with tuberculosis half century ago (Poland)[22] and less common in countries where tuberculosis was less common that time (Japan)[23]. Comparison of consecutive data from observational studies (ELCAP, NY-ELCAP and I-ELCAP) shows that the rate of false-positive results decreases in subsequent studies, which can be explained by growing experience of radiologists which resulted in protocol change. According to International Early Lung Cancer Action Program (I-ELCAP) protocol, only solid lesions at least 15 mm in diameter require immediate evaluation [positron-emission tomography (PET-CT), biopsy], while in most earlier studies tumors at least 10 mm in diameter were send for an immediate evaluation.

Decision trees developed by I-ELCAP are different for baseline and annual screenings and are designed to minimize the risk of unnecessary repeat LDCT in order to improve cost-effectiveness. Figure 1 shows steps for a new patient during the first year after the baseline screening, whereas Figure 2 shows steps for the subsequent annual screenings[13].

Results of meta-analysis presented in Table 1 show that 96% of neoplasms diagnosed with LDCT are non-small cell lung cancers (NSCLC), and only 4% are small-cell lung cancers (SCLC). According to data from the Table 1, about 86% of NSCLC diagnosed with screening are stage I disease.

Another way to convince decision-makers to support LC screening programs are pharmacoeconomical analyses, which aim to find out whether LC screening is cost-effective. The most important parameters which are measured in these studies are incremental cost-effectiveness ratio (ICER) and an incremental cost per quality-adjusted life-year (QALY) gained, which is the cost of prolonging the life of a patient by one year. In most countries, the new medical procedure is believed to be cost-effective when cost per QALY is less than 3 times growth domestic product (GDP) per capita[24]. Cost-effectiveness analyses have to be performed separately for every country (and maybe even bigger region), not only because GDP per capita is different, but also because rate of lung cancer, rate of other pulmonary diseases than lung cancer (for example tuberculosis), methods of calculation and reimbursement of medical expenses, prices for medical procedures and medicines vary between countries. It must be stressed, that prices of medicines (chemotherapy) and radiotherapy are similar throughout the World, regardless of the wealth level of a country, unlike prices of surgery, LDCT and follow-up which are lower in countries where labor is less expensive. Therefore, paradoxically, LDCT screening for lung cancer can be more cost-effective in middle-income than in high-income countries. During the last decade, prices of LDCT screening procedures decreased, similarly as it has happened to prices of all CT procedures in market-oriented economies, unlike prices of medical treatment of advanced cancer which tend to grow because of development of new medicines.

An important parameter for calculation of cost-effectiveness is lead time. Lead time is a time span between detection of cancer with a screening

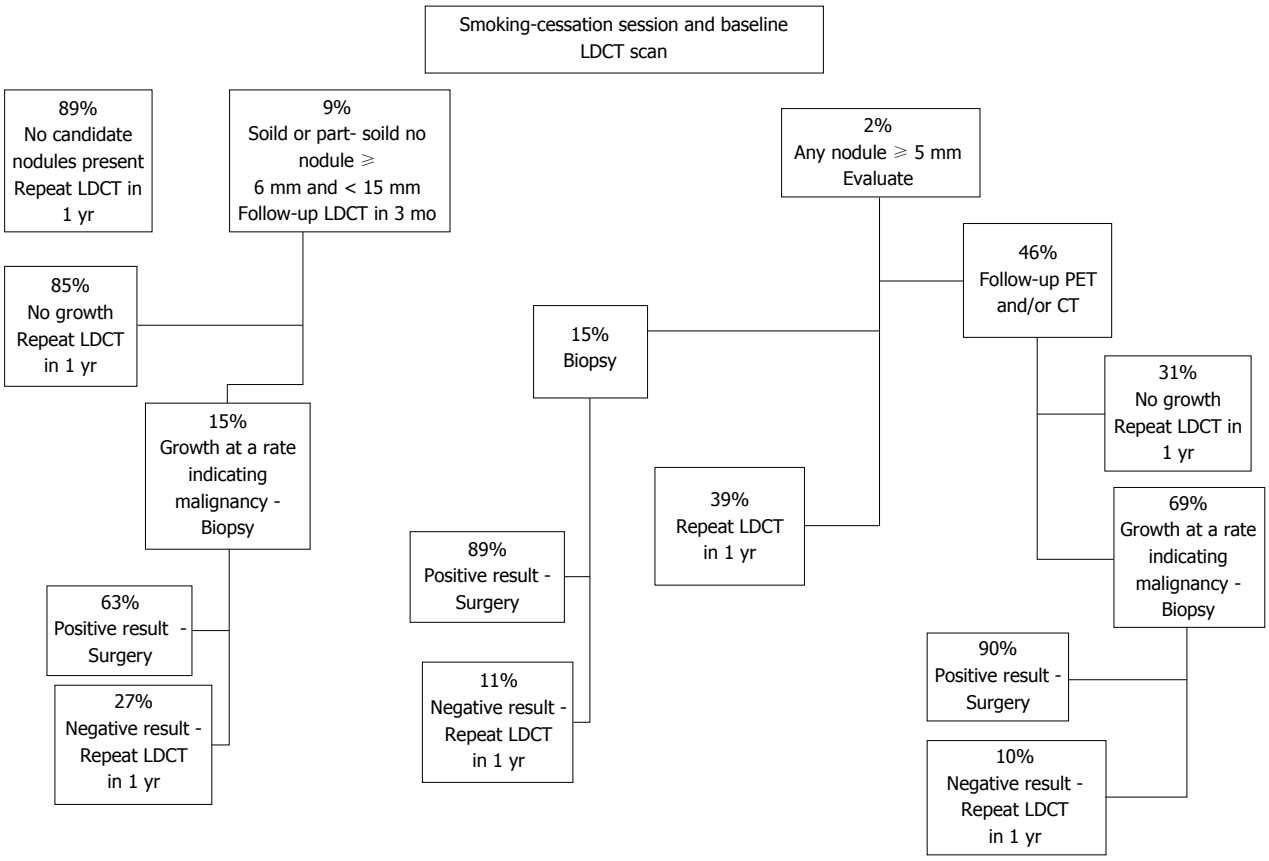

Figure 1 Decision tree within one year after baseline screening[13]. LDCT: Low-dose computerized tomography.

procedure and time when cancer would have been discovered without screening. It is often assumed that lead time for NSCLC cancer is about 3 years, *e.g.,* 6 doubling times (with assumption, that doubling time is 180 d)[14]. However, even without screening, most curable LC cases are detected before onset of clinical manifestations, by radiological procedures performed due to other reasons (*e.g.,* in follow-up CT-scans performed due to other cancers, after chest injuries, due to cardiac chest pain, pneumonia, *etc.*). In such cases lead time is much shorter than 3 years, usually it can be assumed that it is equal zero. On the other hand, solid pulmonary adenocarcinomas or SCLC can develop metastases and become unresectable and incurable even when the primary tumor is less than 5 mm in diameter. In such cases lead time is also zero. On the other hand, lead time can be even longer than 3 years in slowly growing cancers, especially peripheral squamous cell carcinoma and subtype A and B adenocarcinomas, according to Noguchi classification (pre-invasive adenocarcinoma, which grows not as a solid tumor but grows in interfollicular spaces creating so-called ground-glass opacities on chest CT scans)[25]. Therefore, it is questionable whether lead time should be as long as 3 years. We believe that the assumption that lead time for LC is 3 years is either not necessary at all or lead time should be decreased.

Results of cost-effectiveness analyses concerning LDCT for LC are equivocal. In our data which are ahead of print[26], ICER calculated for year 2008 prices was about $1575. The borderline cost-effectiveness of medical procedure in Poland is set at 3 times GDP (gross domestic product) per capita per one year of life gained. In year 2014 it was 27845.25 EUR[24], therefore the implementation of low-dose chest CT for screening of LC is cost-effective. This is similar to results of the study from Israel, where QALY gained was $1464[27]. On the other hand, in the study performed in Australia cost per QALY gained depended upon age of participants and number of pack-years of cigarettes smoked, and varied from Aus$32617 to Aus$114056, and authors concluded that LC screening with LDCT is not cost-effective[28].

Cost-effectiveness analysis of the National Lung Screening Trial performed in the United States varies depending upon methods used. While some authors calculated that the additional cost of screening to avoid one LC death is $240000[29], later calculations performed by the similar group of authors but after administration of different methods found LC screening with LDCT as highly cost-effective, at cost per QALY gained less than $19000[13,30].

CONCLUSION

Comparison of cost-effectiveness analyses allows to formulate the conditions that must be met in order to achieve high profitability of LC screening. The

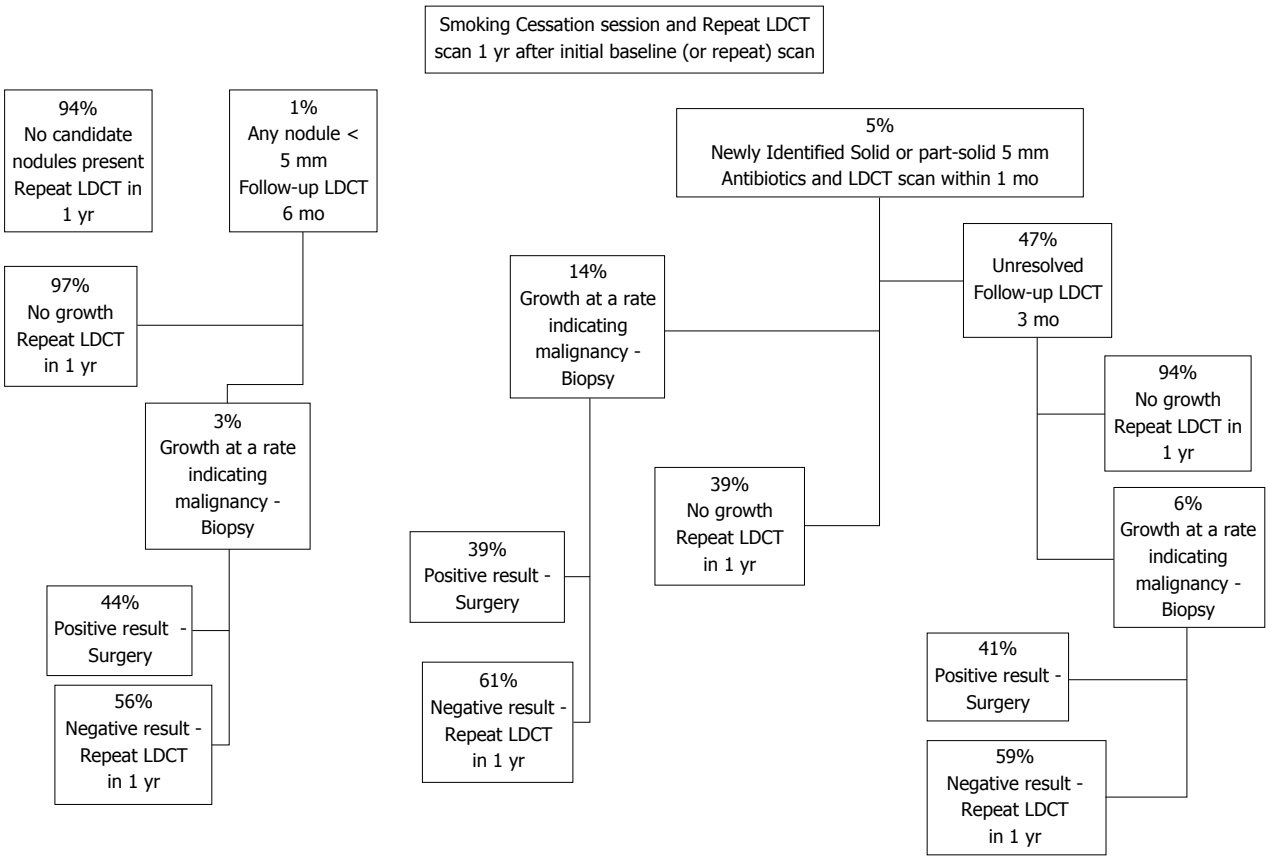

Figure 2 Decision tree one year after initial baseline or repeat scan[13]. LDCT: Low-dose computerized tomography.

first condition is careful formulation and observance of inclusion and exclusion criteria for the screening program which will ensure that screening will be performed only in high risk population, excluding patients who are not suitable for radical surgical treatment. Currently it seems that to ensure high cost-effectiveness, screening should be addressed to participants at least 55 years old, suitable for surgery, who smoked at least 20 pack-years and quit smoking not more than 20 years ago. Secondly, LDCT should be performed in specialized centers where radiologists are trained in detecting early LC and differentiating it from benign lesions, which would minimize the risk of false-negative and false-positive results. Thirdly, radiologists should be equipped with modern computerized programs allowing to analyze changes in nodule volume, which will decrease the number of repeat LDCT, ideally to only one procedure. Taking into account a Japanese experience, it should also be recommended to organize specialized screening centers, dedicated to performing screening procedures according to protocol, *e.g.*, in accordance with inclusion and exclusion criteria. Before such centers are organized, following inclusion and exclusion criteria could be ensured by performing LDCT screening for detection of LC within non-randomized clinical trials. Comparison of cost-effectiveness analyses from Australia, US, Israel and Poland shows that LC screening can be more cost-effective in developed, middle-income countries, where prices of chemotherapy and radiotherapy are similar to those in high-income countries, but cost of labor (*i.e.*, cost of screening, surgery and follow-up) is lower.

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