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Retrospective assessment of Lung-RADS® performance in the Silesian Lung Cancer Screening Pilot Study

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ABSTRACT

Background. A high percentage of false positive results, observed in lung cancer screening studies with low-dose computed tomography (LDCT), caused the modification of radiological assessment methods. According to the International Early Lung Cancer Action Program (IELCAP) all non-calcified nodules with a dimension ≥ 4 mm were considered as positive. Implementation of classification the Lung CT screening Reporting and Data System (Lung-RADS®) recommends additional testing only for nodules ≥ 6 mm, which reduced of false positive results.

Methods. We provided a retrospective analysis of 601 LDCT scans, in asymptomatic volunteers of Pilot Silesian Study of Early Lung Cancer Detection, with at least 20 pack-years of cigarette smoking. The analysis of non- and invasive interventions was done. Assessment of nodules according to the Lung-RADS® system was done. Then the percentage of interventions that could be avoided using the Lung-RADS® criteria was estimated.

Results. In total, 1016 nodules were identified in 265 participants. The positive result of screening was defined as a presence of solid or part-solid nodule ≥ 5 mm and ≥ 8 mm in the case of a nonsolid nodule in line with the IELCAP protocol. Screening based on the IELCAP protocol resulted in 200 positive results and based on Lung-RADS® in the 116 positives. The frequency of lung cancers among participants with a positive result was 7 of 200 (4.0%) (95% CI: 1.0%, 6.0%) for IELCAP and 7 of 116 (6.0%) (95% CI: 2.7%, 9.3%) for Lung-RADS®. The Lung-RADS® criteria reduced number of non- and invasive procedures by 48.8% and 24.1%, compared to IELCAP protocol.

Conclusions. Adopting the Lung-RADS® classification system may reduce harms and improve the efficiency of lung cancer screening programs.

Key words: lung nodules, lung cancer screening, low dose computed tomography (LDCT), Lung CT Screening Reporting and Data System (Lung-RADS®)

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Introduction

Cancer is a leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018. Screening programs aimed at detecting lung cancer target high-risk persons who need consistent monitoring to enable early diagnosis of the disease. The recommended screening test for lung cancer is low-dose computed tomography (LDCT) for persons who are at high risk of lung cancer because of cigarette smoking history and age [1]. In the case of detection of a pulmonary nodule, additional evaluations are needed to determine whether lung cancer is present. Screening protocols standardise interpretation of screen-detected nodules and harmonise nodule management. The International Early Lung Cancer Action Program (IELCAP) and the Lung CT screening Reporting and Data System (Lung-RADS®) are two protocols for lung cancer screening programs [2, 3]. The primary evidence of lung cancer screening effectiveness came from the National Lung Screening Trial (NLST) conducted without a protocol for management

of nodules [1]. The IELCAP showed that increased nodule size cut-offs decreased the fervency of positive results in the baseline screening, with only a few missed cancer cases [2, 4] in comparison to the method used in the National Lung Screening Trial [1]. It substantially reduced diagnostic workload. Most recently, the American College of Radiology introduced the Lung-RADS® protocol to reduce the frequency of false-positives without a significant effect on screening sensitivity [3, 5].

Population oriented screening for lung cancer has significant socio-economic consequences, especially for big countries with large populations of smokers. In Poland, there are about 8.7–9 million smokers (31% of adult men, of whom 26% smoke regularly, and 21% of adult women, of whom 17% regularly smoke) per 38.4 million inhabitants [6, 7]. Such a large-scale screening is a complex organisational challenge and is associated with both benefits and harms. Planning a screening program requires an optimal balance between the benefits, harms, and/or cost-effectiveness. Among many factors, categorisation of many small pulmonary nodules as negative screens substantially reduces the number of false-positives and the subsequent need for additional scans and invasive procedures.

The Pilot Silesian Study for Early Lung Cancer Detection with LDCT used IELCAP as the screening protocol [8]. To assess how the increase of the nodule size threshold would affect screening performance, we retrospectively applied Lung-RADS® criteria to nodule-level baseline results of the screening.

Material and methods

The Pilot Silesian Study included 602 asymptomatic adults with a history of tobacco smoking of at least 20 pack-years and former smokers who quit smoking within the last 15 years before the study visit. In our protocol 20 pack-years was adopted as the cut-off point, due to the inclusion in the cohort of people additionally exposed to other factors, *e.g.* occupational (miners, asbestos workers, steel workers) and environmental (air pollution in the areas of Upper Silesia). One patient was excluded from analysis because of a diagnosis of symptomatic lung cancer. In one patient the cancer diagnosis was missed due to false-negative result of screening [8]. At baseline, the positive result of screening was defined as the presence of a solid or part-solid nodule ≥ 5 mm, and ≥ 8 mm in the case of a nonsolid nodule, in line with the IELCAP protocol [2]. The sizes for nodules were computed based on the measurements performed in two transverse sections. Positive results were followed up with subsequent scans and different invasive procedures (*e.g.* bronchoscopy, endobronchial ultrasound-guided biopsy, transthoracic biopsy) aiming for lung cancer verification (true-positive). Other nodules confirmed in histopathological analyses as benign lesions were defined as false-positive results of screening [8]. In this analysis, we focused on the first-round results; the algorithm of the procedure is presented in Table 1.

To assess the effect of the Lung-RADS® protocol on the performance LDCT screening in the Silesian Pilot Study [8], the criteria of the screening protocol [3] were retrospectively applied to nodule-level data and compared with the primary IELCAP protocol-based data. The comparison included some imaging and invasive procedures performed within alternative screening protocols, sensitivity, and specificity of protocols. Sensitivity was the percentage of screenings with cancer present that were positive; specificity was the percentage of screenings with cancer absent that were negative. The comparison was limited to the results of the baseline LDCT scans.

Results

The Pilot Silesian Study database lists in total 1016 nodules with a diameter ≥ 3 mm detected in 265 persons during the baseline screening. In this set 110 solid, 46 part-solid, and 44 nonsolid nodules were classified as positive results according to the IELCAP protocol. When the Lung-RADS® protocol was applied, the number of positive screening results decreased to 73 solid, 19 part-solid, and 24 nonsolid nodules.

Table 1. Algorithm of the work-up procedures based on the IELCAP protocol

Detected lesion	Recommended LDCT interval or further work-up
SPN ≤ 5 mm	LDCT in 12 months
SPN 6–7 mm	LDCT in 6 months
SPN 8–14 mm solid or part-solid	LDCT in 3 months
SPN ≥ 15 mm	— CT-PET — Biopsy (CT- or US-guided TTNB, EBUS-TBNA, rEBUS-TBNA) — Suspected infectious lesion; antibiotic course; f/u LDCT in 1 month
Intrabronchial SPN	Bronchoscopy

LDCT negative result — further CT not required in the pilot study
LDCT positive result — one solid or partsolid nodule ≥ 5 mm or one nonsolid nodule ≥ 20 mm (annual screening with LDCT in 12 months)

Table 2. Diagnostic procedures with the IELCAP and Lung-RADS® protocols

	IELCAP protocol, n	Lung-RADS® protocol, n	Avoided positive screenings/procedures, n (%)
Number of positive screening results	200	116	84 (42.0)
Follow-up chest CT scans	58	28	30 (48.8)
Bronchoscopy	16	11	5 (31.2)
Endobronchial ultrasound	5	4	1 (20.0)
Transthoracic biopsy	8	7	1 (12.5)

Lung cancer was diagnosed in seven patients after the baseline screening. In one patient two independent, synchronous cancers were diagnosed (large-cell carcinoma and small-cell lung carcinoma). The malignant lesions had an average diameter of 20.25 mm. All were solid nodules. It the case of one person a 15 mm solid nodule was missed at baseline screening and detected in the subsequent scan (false negative result). A change in the scanning protocol from IELCP to Lung-RADS® did not result in changes in the number of true-positive cancer cases or missed (false negative) malignant lesions.

Screening based on the IELCAP protocol resulted in 200 positive results and based on Lung-RADS® in the 116 positives. Both screening protocols had the same sensitivity of 87.5%, and the Lung-RADS® protocol had higher specificity of 81.8% compared to 67.5% in IELCAP. The frequency of lung cancers among participants with a positive result diagnosed in the baseline LDCT scan (positive predictive value) was 7 of 200 (4.0%) [95% confidence interval (CI): 1.0%, 6.0%] for IELCAP and 7 of 116 (6.0%) (95% CI: 2.7%, 9.3%) for Lung-RADS®.

Each positive screening result indicated the necessity of follow-up with the use of noninvasive and/or invasive procedures aiming for further monitoring of detected nodules and diagnosis. Table 2 shows screening-resultant diagnostic procedures performed according to the IELCAP protocol and in the case of use of the Lung-RADS® protocol. The lower number of false positive screening results under the Lung-RADS® protocol allowed us to avoid some diagnostic procedures in comparison to IELCAP. Use of the Lung-RADS® criteria allowed us to reduce the number of noninvasive procedures by 48.8% and invasive procedures by 24.1%, compared to IELCAP-based screening at baseline. Avoidance of subsequent procedures concerned persons with nodules of the second category (13 noninvasive and two invasive procedures avoided) and category 3 (17 noninvasive and three invasive procedures avoided).

Discussion

In cases of malignant nodules, the early diagnosis of lung cancer could provide a safe and definitive solution. Understanding the clinical significance of numerous detected pulmonary nodules in population-level screening initiatives is an important challenge of their optimal management, reducing harm, and financial aspects.

The current analysis addressed the relevance of the nodule size on the performance of two lung cancer screening protocols. Screening based on the IELCAP protocol showed that the risk of malignancy in solid nodules < 5 mm diameter is ≤ 1% [4]. In the Lung-RADS® protocol, solid and part-solid nodules < 6 mm are indicated as benign appearance, with < 1% chance of malignancy and with follow-up after 12 months [5, 9]. Applying the Lung-RADS® protocol to the IELCAP-based screening results reduced the number of false-positive results with no decrease of sensitivity. It suggests better performance for Lung-RADS® than IELCAP as an element of LDCT screening. The previous study showed a similar effect on the false-positive result rate when Lung-RADS® criteria were applied to the results of the National Lung Screening Trial [8]. However, in contrast to the current analysis, sensitivity also decreased in that study, increasing the risk of false-negative results under the Lung-RADS® protocol [8]. All pulmonary nodules identified in the Silesian Pilot Study were large lesions categorised as 4B at baseline scans, with > 15% risk of cancer. There was a two-fold difference between the average diameter of malignant lesions identified in the National Lung Screening Trial and the Silesian Pilot Study (9.9 *vs*. 20.2 mm), which explains the lack of increase in the rate of false negative results in the current analysis. There is an urgent need to adapt the European and American guidelines and recommendations to Polish conditions and consider the possibility of implementation of a lung cancer screening program [10].

Use of the Lung-RADS® protocol may significantly reduce the burden of procedures. In most persons with nodules of categories 2 and 3 it was possible to avoid subsequent chest computed tomography exams and bronchoscopies. Overall it was possible to avoid almost half of the noninvasive and every fourth invasive procedure/s after the baseline screening. Reducing the number of unnecessary follow-ups is important, especially in countries with many potential candidates

for the screening program and its associated significant financial effort.

It is important to note the limitations of the analysis. The major limitation is that the analysis was retrospective and performed on a relatively small sample size compared to other screening prospective studies [1]. There is a potential measurement inaccuracy leading to variability in the size of nodules. The analysis was limited to the baseline screening; thus, conclusions should be limited to the initial screening. It is not only nodule size that drives its management but also the volume and growth rate, which can be measured in a series of subsequent scans [11].

Adopting the Lung-RADS® classification system may reduce harm and improve the efficiency of lung cancer screening programs. The initial observation of the advantages of the Lung-RADS® protocol should be confirmed in a prospective setting.

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Conflict of interest

None declared.

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