ORIGINAL ARTICLE
LUNG CANCER

Surgically treated lung cancer patients: do they all smoke and would they all have been detected with lung cancer screening?

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ABSTRACT Since publication of the National Lung Cancer Screening Trial (NLST) results early lung cancer detection has been widely studied, targeting individuals based on smoking history and age. However, over recent decades several changes in lung cancer epidemiology, including risk factors, have taken place. The aim of the current study was to explore smoking prevalence among lung cancer patients who had been treated surgically or undergone a diagnostic operation and whether these patients would have met the NLST inclusion criteria.

All patients operated on for lung cancer in a university hospital in Estonia between 2009 and 2015 were included. Data were collected from hospital records.

426 patients were operated on for lung cancer, with smoking history properly documented in 327 patients (87 females; median age 67 years). 170 (52%) patients were smokers, 97 (30%) patients were ex-smokers and 60 (18%) patients were nonsmokers. The proportion of females among smokers was 15%, among ex-smokers was 9% and among nonsmokers was 87%. 107 of our patients would not have met the NLST age criteria and 128 of our patients would not have met the NLST smoking criteria. In total, 183 patients (56% (79% of females and 48% of males)) would not have met the NLST inclusion criteria.

Only half of surgically treated lung cancer patients were current smokers and more than half did not meet the NLST inclusion criteria.

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Many currently surgically treated lung cancer patients, especially females, are not a target for lung cancer screening http://ow.ly/L9wY30kIQW0

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Introduction

Smoking is well acknowledged as the main risk factor for lung cancer, and is estimated to be responsible for 90% of cases in males and 80% of cases in females [1]. However, over recent decades several changes have taken place in lung cancer epidemiology. Adenocarcinoma, replacing squamous cell cancer, has become the most common morphological type of lung cancer [2]. In addition to smoking, several other risk factors, *e.g.* second-hand smoke [3, 4], air pollution [5–7], cooking fumes [8], exposure to indoor radon [9] and comorbidities such as chronic obstructive pulmonary disease (COPD) [10] or previous tuberculosis [11], have become more widely recognised. In recent years, lung cancer has been more frequently diagnosed in nonsmokers [12, 13] and the incidence among females is increasing in many countries [14]. In daily practice we also see that lung cancer patients are no longer limited to elderly males with a long smoking history and it has become harder to recognise patients at highest risk for lung cancer.

Following the publication of the National Lung Cancer Screening Trial (NLST) in 2011 [15], lung cancer screening is being evaluated in many countries. Several cancer organisations in the USA recommend screening high-risk patients [16]. In Estonia, lung cancer screening has not been introduced.

The aim of lung cancer screening is to detect the disease at the earliest possible stage and increase survival through immediate radical treatment. Numerous studies have been conducted or are underway to define the optimal target population and evaluate the effectiveness of an organised programme. The current recommended selection criteria for lung cancer screening are based on age and smoking history. These criteria correspond to the NLST inclusion criteria: age 55–74 years, smoking history ⩾30 pack-years and, if a former smoker, having quit within the previous 15 years [16]. At the same time, the National Comprehensive Cancer Network and the American Association for Thoracic Surgery recommend screening from the age of 50 years and inclusion of smokers with a smoking history ⩾20 pack-years [16]. An ongoing study in Europe, the Dutch–Belgian randomised lung cancer multislice computed tomography (CT) screening trial (NELSON), has applied the widest ranges for patient selection criteria in large lung cancer screening trials: adults aged 50–75 years, who have smoked ⩾15 cigarettes per day for >25 years or ⩾10 cigarettes per day for >30 years and still smoking, or stopped smoking <10 years prior to the study, were considered eligible [17].

The aim of the current study was to explore smoking prevalence among surgically treated lung cancer patients and to evaluate whether these patients would have met the current lung cancer screening criteria.

Patients and methods

A retrospective study was conducted to evaluate all lung cancer patients who had been treated surgically or undergone a diagnostic operation in the Dept of Thoracic Surgery at Tartu University Hospital (Tartu, Estonia) between January 1, 2009 and December 31, 2015. Our department is one of the two lung cancer surgical care centres in Estonia. We perform 50–60 lung cancer operations a year, which accounts for ~40% of the lung cancer operations performed in Estonia. The proportion of lung cancer patients receiving surgical treatment is (and was during the study years) ~20%.

Although the majority of patients in the current study underwent radical lung cancer surgery, patients who had undergone a thoracoscopic operation to establish the morphological diagnosis of lung cancer and patients with cancer defined as inoperable during the operation were also included.

Data on patients' demographic characteristics, smoking history, cancer stage (according to TNM (tumour/node/metastasis) classification [18]), cancer morphology and treatment were obtained from hospital records. A CT scan was performed during diagnostic workup in all patients.

Smoking history was calculated in pack-years. Current smokers were persons who, at the time of the surgery, were smoking daily, occasionally or had quit smoking <1 year ago. Ex-smokers were persons who had quit smoking >1 year ago, but had smoked ⩾100 cigarettes in their lifetime. Nonsmokers were persons who had smoked <100 cigarettes in their lifetime.

Approval for the study was obtained from the Research Ethics Committee of the University of Tartu (protocol number 243/T-23).

Statistical analysis

Descriptive statistics were used to characterise the study sample. The Chi-squared or Fisher's exact test was used to assess associations between the variables of interest. A two-sided p-value ⩽0.05 was considered to indicate statistical significance.

Results

During the study period, 426 patients were operated on for lung cancer, with a fully documented smoking history in 327 (76.8%) of the cases (240 males and 87 females; median (range) age 67 (17–88) years).

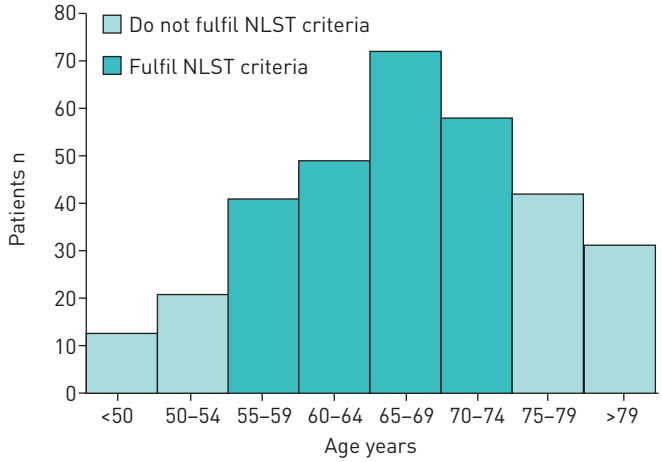

FIGURE 1 Age distribution of 327 surgically treated lung cancer patients stratified by National Lung Cancer Screening Trial (NLST) screening criteria. 107 patients (32.7%) would not have met the NLST age criteria: 34 (10.4%) patients were aged <55 years and 73 (22.3%) were aged >74 years.

Age

34 (10.4%) patients were aged <55 years and 73 (22.3%) patients were aged >74 years, thus altogether 107 (32.7%) patients would not have met the NLST study age criteria for lung cancer screening (figure 1). 13 (4.0%) patients were aged <50 years and 63 (19.3%) patients were aged >75 years, thus altogether 76 patients (23.2%) would not have met the age criteria for the NELSON study.

Smoking

Out of the 327 patients with smoking information available, only 170 (52.0%) were current smokers, while 97 (29.7%) were ex-smokers and 60 (18.3%) were lifetime nonsmokers. The median (range) duration of smoking in current smokers was 40 (10–94.5) pack-years. Among current smokers, the smoking history was <30 pack-years in 31 (18.2%) patients. Among ex-smokers, 28 (29%) patients had a smoking history <30 pack-years; among ex-smokers with a smoking history >30 years, nine patients had quit smoking >15 years ago. Altogether 128 (39.1%) patients (nonsmokers, current and ex-smokers with a smoking history of <30 pack-years, and ex-smokers who had quit >15 years ago) did not meet the smoking criteria of the NLST study for lung cancer screening (figure 2).

As smoking history was recorded in pack-years, and not in number of cigarettes smoked, we were not able to analyse our patients' smoking history according to the NELSON study criteria.

NLST screening criteria

Combining age (<55 and >74 years) and smoking history (nonsmokers, current and ex-smokers with a smoking history of <30 pack-years, and ex-smokers who had quit >15 years ago), altogether 183 (56.0%) of

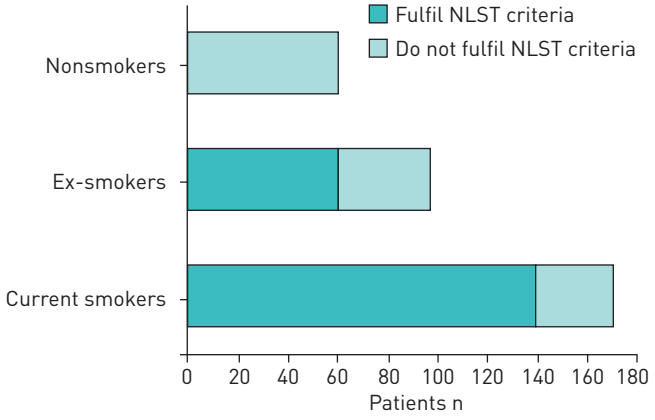

FIGURE 2 Smoking status of 327 surgically treated lung cancer patients stratified by National Lung Cancer Screening Trial (NLST) screening criteria. 128 (39.1%) patients would not have met the NLST smoking criteria: 60 nonsmokers, 37 ex-smokers (38%) who had a smoking history <30 pack-years or had quit smoking >15 years ago and 31 current smokers (18%) who had a smoking history <30 pack-years.

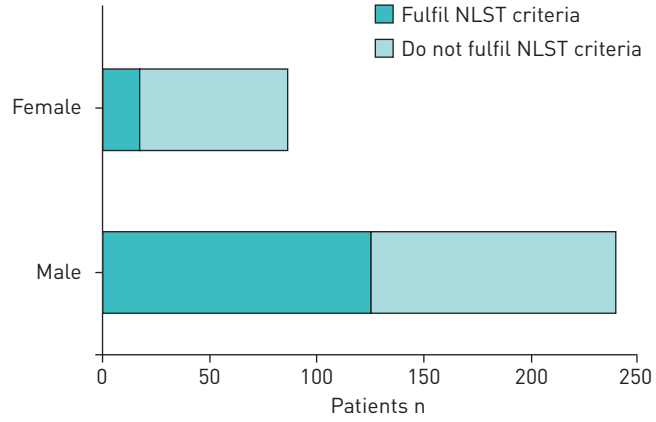

FIGURE 3 Sex of 327 surgically treated lung cancer patients stratified by National Lung Cancer Screening Trial (NLST) screening criteria. 69 females (79.3%) and 114 males (47.5%) would not have met the NLST inclusion criteria.

our patients who were operated on for lung cancer would not have met the NLST study criteria for lung cancer screening.

Sex

We saw statistically significant smoking history differences between male and female patients ($p<0.0001$). Among females, only 26 (30%) were current smokers, while nine (10%) were ex-smokers and 52 (60%) were nonsmokers. Among males, there were 144 (60%) current smokers, 88 (36.7%) ex-smokers and eight (3.3%) nonsmokers.

Analysing males and females separately, 69 of our female patients (79.3%) and 114 of our male patients (47.5%) operated on for lung cancer would not have met the NLST study lung cancer screening criteria ($p<0.0001$) (figure 3). In both males and females, 33% did not meet the age criteria ($p=0.944$); 75% of our female patients and 27% of our male patients did not meet the smoking criteria ($p<0.0001$).

Cancer stage

Cancer stage distribution in our patients at the time of operation is presented in figure 4. The largest proportion of patients (31.8%) had stage IA lung cancer. All stage I–III patients underwent radical lung cancer resection. Stage IV patients included those who underwent diagnostic thoracoscopy (22 patients), had a solitary distant metastasis but were operated on with radical intent (15 patients) and one case that

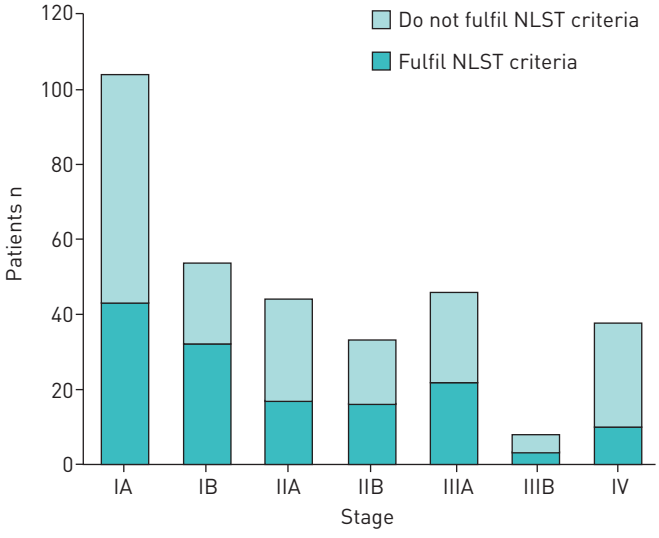

FIGURE 4 Cancer stage distribution of 327 surgically treated lung cancer patients stratified by National Lung Cancer Screening Trial (NLST) screening criteria. 183 (56%) patients would not have met the NLST inclusion criteria, equally distributed between all stages ($p=0.072$).

was defined inoperable during the operation. There was no statistically significant difference between the distribution of patients fulfilling and not fulfilling the NLST criteria in different cancer stages (p=0.072).

Cancer morphology

Morphologically, adenocarcinoma was seen most frequently (166 (50.8%) patients), followed by squamous cell cancer (113 (34.5%) patients), carcinoid (15 (4.6%) patients), large cell cancer (13 (4.0%) patients), small cell cancer (11 (3.4%) patients) and other types (nine (2.7%) patients). Cancer morphology was statistically different when comparing ex-smokers and smokers with nonsmokers (p<0.0001). Among ex-smokers and smokers combined, adenocarcinoma and squamous cell cancer were diagnosed in 45.3% and 41.6% of cases, respectively. Among nonsmokers, adenocarcinoma was diagnosed in 75% of cases and squamous cell cancer in 3% of cases.

Discussion

It is well known that smoking is the main risk factor for lung cancer. However, recent studies have indicated that the proportion of nonsmokers and ex-smokers among lung cancer patients has increased over time. A study in France demonstrated that in 2010, compared with 2000, male lung cancer patients were more frequently never-smokers (4.7% *versus* 2.5%; p<0.0001), active and former smokers were less commonly heavy consumers (43.7 *versus* 45.1 pack-years; p=0.003), and in former smokers the duration of smoking had decreased (34.8 *versus* 35.8 years; p=0.007) and the duration of cessation had increased (15.3 *versus* 11.4 years; p<0.0001) [19].

In our study population (mainly early-stage lung cancer patients, treated surgically) the proportion of nonsmokers was 18.3%, ex-smokers 29.7% and current smokers only 52%. Analysing male and female patients separately, we saw that 60% of females were lifetime nonsmokers, whereas only 3.3% of males fell into this category. Other researchers have also demonstrated sex differences in the role of smoking in lung cancer development [20, 21]. In the NLST study population, 59% were male and 41% were female [5] compared with 73% and 27%, respectively, in our study population. Similar male predominance is typically observed in surgical lung cancer studies [22, 23].

Currently, lung cancer is diagnosed at an early stage, when surgical treatment (*i.e.* the most effective treatment modality) is still applicable, only in a minority of cases. Thus, to improve the treatment results, early detection of lung cancer through screening would be more than justified. According to a recent study, only 26.7% of subjects diagnosed with lung cancer in the USA would have met the NLST eligibility criteria [24]. As NLST had demonstrated a 20% lung cancer mortality reduction in the study population, in the total US population this would translate into only ~5% reduction in lung cancer mortality [24]. According to Pinsky and Berg [24], to achieve this modest benefit, 6% of the population aged >40 years should be screened for lung cancer. Expanding the age range and smoking criteria, the number of cancer cases detected would increase, but so would the size of the population to be screened [24].

In our study, we were able to demonstrate that when applying the NLST screening criteria, we would have been able to detect lung cancer in 44% of the surgically treated lung cancer patients. However, based on age and/or smoking history, many of our patients would not have qualified for the screening. Currently, more and more elderly patients, including octogenarians, receive efficient surgical treatment for lung cancer [23, 25]. Thus, an upper limit for age (alone) should probably not be set. Elderly individuals could be assessed, as before any surgical intervention, for fitness for the potential radical treatment and only when fit continue in the lung cancer screening programme. In addition, the increase of lung cancer incidence among nonsmokers, especially females, needs to be considered when planning future screening studies. Other risk factors, such as previous history of lung cancer or tuberculosis, COPD, or exposure to radon or other carcinogens, are currently not taken into account when selecting individuals for lung cancer screening. Further studies are needed to establish their role among lung cancer screening criteria.

Limitations

The limitation of our study was the retrospective nature, which did not allow us to record smoking habits in more detail (*e.g.* in number of cigarettes smoked per day). Smoking information had been collected as part of the routine medical history at hospital admission and was self-reported, but missing in a quarter of the patients. We could have been more confident in the conclusions drawn had a detailed smoking history been available for all of the patients. Although this was a single-centre study, it included ~40% of patients operated on for lung cancer in Estonia.

Conclusions

In conclusion, while screening is a promising tool for detecting lung cancer at an early stage and thereby improving survival, our study demonstrated that half of lung cancer patients might not be captured by

screening when following the NLST criteria. In particular, female nonsmokers and older male smokers, currently not targeted by lung cancer screening, yet constituting a considerable proportion of patients operated on for lung cancer, should be carefully considered.

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