From the IASLC Early Detection and Screening Committee

Lung Cancer Screening Considerations During Respiratory Infection Outbreaks, Epidemics or Pandemics: An IASLC Early Detection and Screening Committee Report

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# Abstract

After the results of two large, randomized trials, the global implementation of lung cancer screening is of outmost importance. However, COVID-19 infections occurring at heightened levels during the current global pandemic, and also other respiratory infections, can influence scan interpretation, and screening safety and uptake. Several respiratory infections can lead to lesions that mimic malignant nodules and other imaging changes suggesting malignancy, leading to an increased level of follow-up procedures or even invasive diagnostic procedures. In periods of increased rates of respiratory infections such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) there is also a risk of transmission of these infections to the health care providers, the screenees and patients. This became very clear and evident for the SARS-CoV-2 pandemic and led to a temporary global stop of lung cancer and other cancer screening programs. Data about the optimal management of these situations are not available. The pandemic is still ongoing and there will come further periods of increased respiratory infections, where practical guidance would be helpful.

The aim of this report is a) to summarize the data available for possible false positive results due to respiratory infections, b) to evaluate the safety concerns for screening during times of increased respiratory infections, especially during a regional outbreak or an epidemic or pandemic event, c) to provide guidance for these situations and d) to stimulate research and discussions about these scenarios.

# Introduction

Lung cancer screening using low-dose computed tomography can reduce lung cancer specific mortality (1, 2). Widespread implementation of lung cancer screening can have a major impact on this major public health problem. However, there are several issues to face, like finding necessary resources, selecting and recruiting the right persons. Furthermore, subacute and chronic respiratory infections and especially epidemic and pandemic respiratory infections influence safety and uptake of lung cancer screening as well as scan interpretation and work-up of findings, The current Coronavirus disease 2019 (COVID-19) pandemic emphasized once more the necessity of protective measures against respiratory infections transmitted via droplets and aerosols. This led to the acute prioritization of health care resources including initially scarce special pathogens personal protective apparel for health care workers who cared for the rapidly increasing number of COVID patients around the world, necessitating a reduction in health care resources to all but emergency and urgent clinical scenarios in many parts of the world. For example, in the United States the volume of CT examinations fell by 53% at the nadir within a month after emergency declarations in March 2020, returning to 84% of prior volumes by September 2020 (3, 4). Reduction of health care resources limited the availability of lung cancer screening, diagnostic and therapeutic measures, which translated into a reduction of the number of newly diagnosed lung cancer cases (5, 6). It might be speculated that the COVID-19-related delays in screening and early diagnosis of lung cancer may lead to a shift to a greater proportion of patients with advanced stage disease (7). Furthermore, the pandemic served as a reminder that respiratory infections can mimic the symptoms of lung cancer, necessitating additional follow-up examinations. In this manuscript we aimed to collate and analyse data about these aspects and provide guidance how we can handle these challenges.

# Possible pitfalls in the detection of malignancy in respiratory infected individuals

Acute bronchopulmonary infection or inflammation can simulate malignant processes and can be a source of false positive results on chest computed tomography (CT) and FDG-positron emission tomography CT (PET-CT) (8-10). In the Dutch-Belgian randomized NELSON lung cancer screening trial with Low-Dose Chest CT (LDCT), approximately 10% of solid, intermediate-sized, pulmonary nodules found at baseline screening resolved during follow-up (11). Three-quarters of these findings disappeared on the 3-month follow-up LDCT examination, suggesting resolution of a prior acute infectious or inflammatory process. Review of the International Early Lung Cancer Action Program (I-ELCAP) database showed that up to 70% of new nodules found on annual or baseline screenings resolved on short-term follow-up CT (12). Similarly, in a retrospective analysis from the lung cancer screening programme at the Massachusetts General Hospital, suspected acute infectious or inflammatory lung abnormalities were seen in 8.7% of the screened participants (13). 87.5% of these changes resolved on follow-up. The clinical significance of a solitary pure or mixed ground-glass opacity nodule of less than 3 cm on chest CT was analysed in a trial from Korea, with 37.6 % of the pure ground-glass opacity lesions and 48.7 % of the mixed lesions becoming smaller or resolving on follow-up high-resolution CT (HRCT) (14). Lastly, Hussaini and colleagues reported that during the 2015/16 and 2016/17 flu seasons, 16.5 % and 11.9 % of the lung cancer screening participants needed a short-term follow-up CT, of which 84 % and 80 % of these findings respectively resolved, suggesting infection or inflammation (15). The difference in the proceedings was that the staff started to ask individuals undergoing lung cancer screening if they had signs or symptoms of a recent or current respiratory illness prior to their appointment and if present, rescheduled these screenings to 6 to 8 weeks later, in order to reduce the frequency of false positive exams. In Vancouver, Canada, prior to the COVID pandemic, among 1,326 participants in the screening study between March 2019 and February 2020, 10.3% of them had early recall LDCT within 3 months for lung abnormalities. Fifteen percent of them were found to have lung cancer. During the COVID pandemic, 874 people were screened between March 2020 to February 2021 with 18.5% of them required early recall LDCT for lung abnormalities and only 3.7% of them were found to have lung cancer. Therefore, in times of increased respiratory infections, respiratory infections may lead to an increased rate of false positive screening results with negative consequences for the screenees and increase in health care resource utilization.

It is known that various vaccinations in the upper arm can cause primarily ipsilateral axillar lymph node enlargements, which can also be FDG-PET positive (16). Regarding the vaccinations against CoViD-19 more literature about these findings is available. This led to the recommendation: an interval of 6 weeks between vaccination and imaging is advisable (17, 18).

We therefore recommend to ask the screening participants before imaging, whether they have acute respiratory symptoms or got vaccinated on the upper arm and, if this is the case, to postpone the screening LDCT or PET scan by 6 - 8 weeks to minimize unnecessary follow-up examinations. Respiratory infections may – especially in times of increased respiratory infections – lead to an increased rate of false positive screening results with potentially harmful consequences for screenees and screening programs. Vaccinations can cause unnecessary follow-up examinations.

Apart from acute infections and inflammations, subacute infections and chronic disease states can simulate malignancy. For instance, pulmonary tuberculosis can cause nodules, and these can be FDG avid (19, 20). In the Korean Lung Cancer Screening Project, tuberculosis sequelae resulted in a reduced specificity of CT screening for lung cancer using the Lung CT Screening Reporting and Data System (Lung-RADS) (21). Underlying pulmonary illnesses, that increase the risk of infections, such as bronchiectasis, may also have an impact on lung cancer screening programs. The prevalence of bronchiectasis in participants in lung cancer screening programs has been analysed in two different studies of I-ELCAP sub-cohorts (22, 23). Using different scales, 11 % and 23 % of the participants from Pamplona and New York, respectively, had bronchiectasis on their LDCT. In the Spanish study, individuals with bronchiectasis more frequently had lung nodules and a greater proportion of them were not cancer (22). These differential diagnoses lead to an increased level of follow-up imaging studies or even invasive diagnostic procedures. Therefore often, in clinical practice – if infection is a possible differential diagnosis – antibiotic treatment and a follow-up CT is recommended. In areas with high prevalence, active tuberculosis should be considered as differential diagnosis and has to be addressed in screening programs.

# Effects of the COVID-19 pandemic on lung cancer screening and lung cancer management

The acute phase of the COVID-19 pandemic led to a shutdown of most screening programs in the respective regions and reduced diagnoses of cancer (7, 24-26). Furthermore, most research programs in lung cancer screening were also largely suspended in many parts of the world. However, the situation was inconsistent in various regions of the world. In April 2020, during the peak of the pandemic incidence, screenings for lung cancers in the USA were lower by 56%, in comparison to the same period in 2019 (25). For instance, the programme at the Massachusetts General Hospital reported a decrease in the average weekly volume of LD screening CTs by 74 % from the pre-COVID peak period to the COVID peak period (27). By the end of July 2020, the volume had regained to 68 % of average pre-COVID peak weekly numbers. In the whole Massachusetts General Brigham health care system, the number of lung cancer screening tests between March 2 and June 2, 2020 decreased for almost 80 %, in comparison to three control periods (December 1, 2019 to March 2, 2020; March 2, 2019 to June 2, 2019; June 3 to September 3, 2020). The percentage of positivity of the screening test remained at about 0.8 % (26). In an analysis of the lung cancer screening programme of the University of North Carolina Healthcare System from January 1, 2019, to September 30, 2020 a reduction of 33.6% in predicted screening volumes was seen in March 2020 coinciding with the beginning of the COVID-19 pandemic. By June 2020, predicted volumes had already returned to expected pre-COVID-19 levels (28). The US Population-based Research to Optimize the Screening Process (PROSPR) consortium surveyed the effect of the pandemic on several screening programmes in eight health care systems in seven states (29). Screening for lung cancer decreased in April and May 2020 by 62 %. Within the American College of Radiology’s Lung Cancer Screening Registry, a 54% reduction in screening volume across the United States was observed between March and May 2020 compared to the same months in 2019. Screening activity rebounded in the latter half of 2020. In the not yet verified analysis the year over year volume was only down by 1.5%. It should be noted that the year over year growth was 28% prior to the pandemic (30).

In July 2019, the National Health Insurance System of South Korea launched a National Lung Cancer Screening program for the high-risk population. Although there was a COVID -19 outbreak in South Korea, the National Lung Cancer Screening program had been progressing without any drawback. However, the screening rate has decreased from 23.7 % in second half of 2019 to 22.4 % in entire year of 2020.

In the UK, a number of innovative implementation lung cancer screening health checks have been underway since the publication of the United Kingdom Lung Cancer Screening (UKLS) trial (31). The Liverpool Lung Health Project was initiated in 2016 (32), followed by the Manchester Lung Health Check (33), West London Cancer Screening pilot (34), and the Yorkshire Lung Cancer screening trial (35). These studies provided the spring-board for the NHS England to provide a major investment to introduce a national programme in 10 new regions (36), this programme utilises two risk prediction models (PLCOm2012 (37) and LLPv2 (38, 39)) to select high risk participants. However, all these programs were stopped in March 2020 with the national COVID-19 lockdown. Some of these restarted in the summer months of 2020, but the NHS programme has been on hold since March 2020, with plans to re-start recruitment again in the summer of 2021.

The situation throughout the world is partly summarized in *Table 1*. In addition to the effects on ongoing screening programs presented in Table 1, the planned introduction of new national screening programs was further delayed in countries such as India and South Africa. Even normal diagnostic and therapeutic procedures had to be partly postponed. In China for example, during the pandemic, it was recommended, that if the symptom of fever has improved after treatment, patients with pulmonary nodules should still be in quarantine for another 14 days instead of immediate clinical assessment for the nodules (40). In China it was found that patients with cancer are more susceptible to be infected of the SARS-CoV-2 during the COVID‐19 pandemic, with a consequent poor prognosis (41). In the UK, it has been recognised that lung cancer control has been badly hit by the COVID-19 pandemic (42, 43), Apart from disruption to the diagnostic pathways, treatment pathways were also impacted. Chemotherapy treatments of patients were mainly stopped in light of the immunosuppressive impact and potential side effects. The UKLCC’s Clinical Advisory Group noted an increased mortality of 40-50%, if lung cancer patients contracted COVID-19 following surgery (43).

Moreover, the recent global observational The Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) study suggested that there is high mortality in patients with thoracic cancers who were infected with COVID-19 (44).

# Safety concerns in periods of increased respiratory infections

In periods of increased rates of respiratory infections, there is also a risk of transmission of these infections to the screening staff and to the screenees. This became very clear and evident during the SARS-CoV-2 pandemic and led to a temporary global stop of screening programs. If there is a clearly increased risk in epidemic situations the safety of the staff and the screening participants is of primary concern, but data about the optimal management of these situations are not available. The pandemic is still ongoing and there will come further periods of increased respiratory infections, where guidance would be helpful.

It has been suggested that lung cancer screening can be deferred until the COVID -19 pandemic resolves as it is not likely to have an impact on overall survival (45, 46). This is also the case for more invasive diagnostic approaches (47, 48). However, these recommendations are based on weak evidence and short-term observation. While the effects of prolonged curtailing of lung cancer screening have yet to be determined, it is known that delay in diagnosis and treatment of lung cancer affects the survival of patients (49-51).While an only modest impact on survival may be the case, if the pandemic were short-lived, the prolonged pandemic for over 18 months now and the reduction of resectable early-stage lung cancers observed suggest that we will be seeing more advanced lung cancers in the coming months and years with negative effects on mortality. It is therefore crucial to find a solution to continue lung cancer screening with reduced health care resources taking into account multiple local, regional, and patient-related factors to provide optimal care.

The screening and early detection program includes several steps: the pre-screening phase with selection and invitations of the eligible participants, tobacco cessation counselling for active smokers, pulmonary function tests (pre and post bronchodilator spirometry and diffusion capacity), shared decision making, low dose CT procedure and evaluation, team discussion and at the end in case of suspicious findings a consultation of the patient with a pulmonologist to explain the screening findings. Invasive diagnostic tests such as CT-guided lung biopsy, bronchoscopic procedures or surgery may then be indicated. Some of these steps can in principle be done remotely via online tools or mail. This can apply for checking for eligibility, tobacco cessation counselling, and a consultation with a pulmonologist at the end to explain the screening findings in a varying degree and partly in an online setting. Pulmonary function tests (pre and post bronchodilator spirometry and diffusion capacity) usually have to be performed in practices, outpatient clinics and hospitals and may pose some risk of exposure without proper room ventilation, disinfection and personal protection equipment. This is also true for the low dose CT procedure. The risk usually increases with invasive procedures such as bronchoscopy. In addition safety measures for travelling and hospital visits have to be planned (52).

Depending on the actual risk in the region, strategies that may be considered are:

- Invitation and eligibility assessment as well as counselling about the advantages and disadvantages are done by mail or by virtual health tools.

- The tobacco cessation consultation can be started via videoconferences with telephone or text messaging follow-up.

- If vaccination is available, the vaccination should be completed six weeks before the on-site lung cancer screening takes place.

- If testing for acute infection is available and reliable and is indicted, this can be done before on-site visits.

- Patients should attend the institution during time slots where patient volume is limited, and this can be guided by advanced scheduling.

- Pulmonary function tests should be scheduled after online counselling with a pulmonologist taking into account air exchanges in the room and time to disinfect the equipment and the room. Changing filters in the apparatus for each patient is usually done as standard procedure in lung function testing and should be mandatory in these situations.

- Initial consultation with the pulmonologist can be carried out by telemedicine to reduce the need for in-person visits, once the low-dose CT and lung function tests have been performed.

- Invasive procedures have to be decided taking into account the pre-test malignancy probability and risk of infection according to the actual local infection risks (48).

# Management of back log of screening procedures during and after temporary reduction in activity

In the current COVID -19 pandemic, cancer screening, including lung cancer screening, has been stalled. As in times of reduced activities the usual screening volume cannot be achieved, a back log of required work exists, and mechanisms of prioritizing individuals have to be discussed. This is especially true in regions with limited resources. In this regard, optimal ways to select individuals for lung cancer screening during the COVID -19 pandemic and resumption of screening when the pandemic recedes and for other situations with reduced resources need to be applied. One option is to prioritize individuals with the highest lung cancer risk. This is an approach that is not possible with the categorical age/pack-years/quit-time criteria. It is known that participants with the highest risk statistically benefit most of screening. As selection of these highest risk persons cannot be done by using categorical selection criteria, one option is therefore to prioritize individuals with the highest risk based on a quantitative lung cancer risk prediction model such as PLCOm2012 or the Liverpool Lung Project risk score (53) and – if it is a repeat round - Lung-RADS category or volume doubling time can serve as a guide. Prioritizing screening could be done by rank order of model risk estimates, starting with the highest and working down.

In some jurisdictions, lung cancer screening is starting up again or will do so in the future. In the Ontario Health (Cancer Care Ontario)’s lung cancer screening pilot, which has transitioned into the Ontario Lung Screening Program, lung cancer screening was interrupted in March of 2020 at its four major screening sites, and as the COVID-19 pandemic receded, screening restarted in July of 2020 before it was curtailed again in the second wave of COVID-19. Recommendations were made to sites to prioritize screening starting with those with preceding abnormal Lung-RADS classifications and to those with highest PLCOm2012 scores. There is evidence to support this recommendation. Individuals who screened negative prior to 2009 in the Toronto Princess Margaret site of the International Early Lung Cancer Action Program (IELCAP) were recalled for screening between 2015 to 2018 starting with those with highest PLCOm2012 risk scores and working down the rank order (54, 55). A total of 327 individuals were contacted initially and 200 individuals were scanned who had a median time gap since previous CT of 7 years. Of the 327 individuals, 68 (20.8%) had developed lung cancer during the follow-up period or had lung cancer diagnosed from the follow-up scan (14 of 200 or 7.0%). Twelve of the 14 screen-detected lung cancers were stage I or II. At a later point in the study, 359 individuals had returned for screening. The incidence of lung cancer in those with PLCOm2012 risks ≥ 3.5%/6-years was 11% and in those whose risks were ≥ 2.0% to <3.5% was 1.7% (p=0.002). Similarly, in the Vancouver site of the International Lung Screening Trial (56), of the 2138 individuals, 62 (2.9%) had developed lung cancer. The incidence in those with PLCOm2012 risks <1.5%, ≥1.5 to <3.5% and those ≥ 3.5%/6-years were 1.2%, 2.04% and 6.2%, respectively. The incidence among individuals with a PLCOm2012 risk ≥13.5% was 8.5%. The findings of these studies indicate that those with highest PLCOm2012 risks have the highest proportion of lung cancers, and for this reason their screening should be prioritized.

# Conclusions and Recommendations

Respiratory infections can mimic malignancies in thoracic imaging resulting in false positive findings leading to additional follow-up imaging studies and diagnostic work-up with increased risks to patients and added costs to the health care system. The committee recommends the following measures and strongly encourages a systematic evaluation to provide additional evidence.

Recommendations:

1. Enquire about acute respiratory symptoms by tele-medicine interviews prior to the scheduled visit and in-person before imaging procedures and ask for recent vaccinations in the upper arm. Reschedule these procedures in case of symptoms or recent vaccination for approximately 6 - 8 weeks later. (OCEBM level of evidence level 4 (57))
2. Prior to admission of individuals into screening facilities interview individuals for recent exposures to potentially infected individuals and exposures and require e.g. COVID testing as is appropriate. This is to reduce likelihod of COVID transmission in the screening centre to staff and others. (OCEBM level of evidence level 4 (57))
3. If there is a regional high rate of respiratory infections adapt the screening program to the actual risk level for contracting infections and switch parts of the screening programme to a remote setting. (OCEBM level of evidence level 4 (57))
4. Consider testing for the acute infection and vaccination with a time difference of approximately six weeks for on-site procedures, where available. (OCEBM level of evidence level 3 (57))
5. If there is a back log of screening procedures prioritization of the highest risk groups using a quantitative lung cancer risk prediction model should be considered. (OCEBM level of evidence level 3 (57))
6. Invest in educating the medical staff involved in lung cancer screening programs on specific steps necessary to adapt the procedures according to the situation at hand. (OCEBM level of evidence level 4 (57))

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# Tables and figures

Table 1: Effects of CoViD-19 on lung cancer early detection and screening programs during the first year of the pandemic

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country**  | **Province or program** | **Official governmental restrictions** | **Date / Period**  | **Effect / Consequences on lung cancer screening** |
| **Brazil** | Six institutional screening programs | Yes | April 2020 - present | Stop or delay  |
| **Canada** | Ontario Lung Screening Program | Ontario Health recommendation to Regional Cancer Programs | March – May 2020May - June 2020 June 2020 - present  | DelayGradual restart in descending order for those with the highest PLCOm2012 riskProgram resumed  |
| **China** | Zhongshan Hospital Fudan University, Shanghai, China | Yes | January - February 2020 | Stop  |
| **Colombia**  | Local private practice / special insurance | Yes | April 2020 to December 2020 | Stop  |
| **Germany** | Research programs | Yes | March - September 2020 | Stop  |
| **Hungary**  | Multi-centre pilot programme sponsored by the Ministry of Human Resources | Yes | March – May 2020June 2020 | Delay Gradual restart  |
| **Italy**  | Independent trials or local private practice | Yes | March – June 2020March – May 2020June 2020 | Interruption of enrolment Reduction of follow upsProgram resumed  |
| **Serbia**  | Regional pilot screening program | Yes | March - May 2020June 2020  | StopGradual restart |
| **South Korea** | National Health Insurance Service Screening Program | No | July – December 2019January - December 2020 | Normal screening activityContinuation of screening activitywith a decreased screening rate (23.7% in the second half of 2019 to 22.4% in entire 2020) |
| **Spain** | Two IELCAP screening programs (Navarra, Valencia) | Yes | March – May 2020May 2020 - presentMarch – April 2020April – May 2020May 2020 - present | Clinica Universidad de Navarra: reduced to just a few follow-upsProgram resumedInstituto Valenciano de Oncologia: screening activity stopped Follow-ups resumedProgram resumed |
| **UK** | Liverpool Health Lung Project (32)Manchester Health Check (33)Yorkshire Lung cancer screening trial (35)NHS-Eng-National-Cancer-Programme. Targeted Screening for Lung Cancer(36). | Yes | March 2020 Autumn 2020August 2020July 2020Summer 2021 | StoppedLiverpool Health Lung Project: only short-term follow-up scans and clinical investigationsManchester Health Check: restarted recruitmentYorkshire Lung cancer screening trial: restarted NHS-Eng-National-Cancer-Programme. Targeted Screening for Lung Cancer: planed start of recruitment  |
| **USA** | Mount Sinai Health Care System, New York, NY | Yes | March 15 to June 1, 2020March 15 to May 1, 2020.June 1, 2020 to presentMay 1, 2020 to present | Short term follow-up LDCT scans only Biopsy of nodules for lung cancer not performed Baseline and annual repeat screening: restartedBiopsies of nodules for lung cancer: restarted  |
| **USA**  | Centers for Disease Control (CDC), the American College of Radiology (ACR) Guidance and the ACR Lung Cancer Screening Registry | Yes | March-May 2020April 2020June 2020 – presentJune-September 2020 | Program delay (ACR LCSR screening exam volume is down 54.3% over the same period in 2019)Gradual restart according to CHEST Expert Panel Report on lung cancer screening during the COVID-19 pandemic, stratified by risk of cancer (45)Programs resumed according to CDC and ACR guidance (58); ACR LCSR screening exam volume is down 3.76% over the same period in 2019 (30) |

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