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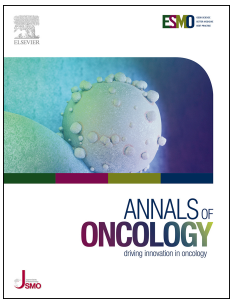

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Hesitancy around low dose CT screening for lung cancer

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Abstract

Lung cancer is the leading cause of cancer death worldwide. The absence of symptoms in early stage (I/II) disease, when curative treatment is possible, results in greater than 70% of cases being diagnosed at late stage (III/IV), when treatment is rarely curative. This contributes greatly to lung cancer's poor prognosis which sees only 16.2% of individuals diagnosed with the disease alive at 5 years. Early detection is key to improving lung cancer survival outcomes. As a result, there has been longstanding interest in finding a reliable screening test. After little success with chest radiography and sputum cytology, in 2011 the US National Lung Screening Trial (NLST) demonstrated that annual Low Dose Computed Tomography (LDCT) screening reduced lung cancer specific mortality by 20%, when compared with annual chest radiography. In 2020, the NELSON study demonstrated an even greater reduction in lung cancer specific mortality for LDCT screening at 0, 1, 3 and 5.5 years of 24% in men, when compared to no screening. Despite these impressive results, a call to arms in the 2017 European position statement on Lung Cancer Screening (LCS), and the widespread introduction across the US, there was, until recently, no population-based European national screening programme in place. We address the potential barriers and outstanding concerns including common screening foes, such as false positive tests, overdiagnosis, and the negative psychological impact of screening, as well as others more unique to LDCT LCS, including appropriate risk stratification of potential participants, radiation exposure and incidental findings. In doing this, we conclude that whilst the evidence generated from ongoing work can be used to refine the screening process, for those risks which remain, appropriate and acceptable mitigations are available, and none should serve as barriers to the implementation of national unified LCS programmes across Europe and beyond.

Keywords: Lung cancer; Screening; Low Dose CT (LDCT); Early detection.

Highlights:

- Lung Cancer Screening (LCS) with Low Dose CT (LDCT) in high-risk individuals reduces lung cancer mortality.
- LCS has been introduced in the US, but few unified, national LCS programmes are in place across Europe.
- Barriers to the widespread implementation of LCS in Europe are well documented with appropriate mitigations available.
- Necessary research is underway across several European counties to address existing barriers and optimise practice.
- Existing barriers should not serve as reasons not to implement national, unified LCS programmes across Europe.

Introduction

As the leading cause of cancer death worldwide there is longstanding interest in finding a reliable screening method for lung cancer. In 2011, the US National Lung Screening Trial (NLST) demonstrated that low-dose CT (LDCT) reduced lung cancer specific mortality by 20%. [1] This resulted in the United States Preventive Services Taskforce (USPSTF) recommending LDCT screening for those at risk across the US, funded by Medicare and Medicaid. Following these results, the European Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) study confirmed similar survival benefit. Despite this, only one European country (Croatia) has implemented a national LCS programme (in 2020), with no further population-based European national screening programmes in place. [2] This article seeks to elucidate the current state of lung cancer screening (LCS), and address some of the existing barriers to its implementation in Europe.

Lung Cancer Mortality: The Size of the Problem

Lung cancer is the single biggest cancer killer worldwide accounting for 18.4% of all cancer deaths. [3] Lung cancer prognosis is poor, with only 16.2% of people alive 5 years after diagnosis. [4] This is largely attributable to the late presentation of disease, due to a relative absence of symptoms in early stages, when curative treatment is available. In the UK only 24-28% of cases are diagnosed at early stage (I-II), and the remaining 72-76% at late stage (III-IV).[5] Survival varies greatly based on disease stage at presentation, with 88% of individuals with stage I disease surviving to one year, compared to 19% of individuals diagnosed with stage IV disease. [4] Therefore, early detection is key.

Initial studies assessing the use of chest radiography and sputum cytology for lung cancer screening found these methods not to be effective. [6] Then, in 2011, the NLST LDCT screening trial was published: the large US-based randomised controlled trial (n=53,454) compared annual LDCT to annual chest radiography and demonstrated a reduction in lung cancer mortality of 20%, and reduction in all-cause mortality of 7% [1]. As a direct result, in 2014, the USPSTF produced grade B guidance recommending annual screening for lung cancer with LDCT in adults age 55-80 years who have a 30 pack year history of smoking, and who currently smoke or have quit within the past 15 years, [7] criteria in line with NLST inclusion. These parameters have recently been widened to adults ages 50-80 who have a 20 pack-year smoking history and who currently smoke or have quit smoking within the past 15 years. If LDCT screening had been implemented across Europe in 2011, following the NLST results, an estimated 295,175 lung cancer deaths could have been prevented (see Figure 1).

Whilst LDCT screening was being rolled out across the US, European countries took a more cautious approach, with many awaiting further mortality data from the NELSON study. NELSON compared LDCT screening at 0, 1, 3 and 5.5 years with no screening. The results published in January 2020 demonstrated a relative risk reduction in lung cancer mortality in the LDCT arm of 24% in men and, although not significant due to

lower numbers recruited, an even greater 33% relative risk reduction in women, [8] further supporting the NLST results.

With researchers and clinicians in agreement that early diagnosis is key to improving the high mortality rates from lung cancer, and repeated evidence in large, randomised studies to support the mortality benefit of LDCT screening, the question remains, why are so few programmes in place across Europe? We look to explore the reasons for this through this article.

Barriers to Screening

For those cautious about endorsing LCS, the potential harms can appear to outweigh the benefits. These concerns include common screening foes, such as false positive tests, overdiagnosis, and the negative psychological impact of screening, as well as others more unique to LDCT LCS, including appropriate risk stratification of potential participants, radiation exposure and incidental findings. And then, crucially for a screening programme that needs a large amount of infrastructure, cost effectiveness and work force considerations. While data exist in LCS trials on many of these issues, studies display substantial heterogeneity in their methods and underlying healthcare structures, making the translation of results between screening populations challenging. But a closer examination of the perceived barriers may help illuminate not just how the data around metrics like false positives can be easily misinterpreted, but also how we may overcome these barriers.

False positives

The distress and added investigations implicit in a false positive result are a deterrent for potential participants and providers alike. Rates of false positive results in LDCT screening have been wildly different, depending on the study or service. The NLST published a rate of 96%, in stark contrast to the UK Lung Screening study (UKLS) rate of 3.6% (which is the same as NELSON). So why the disparity?

A key to understanding these remarkable differences is reflected in what the investigators felt was abnormal and potentially positive. NLST included all pulmonary nodules that required any follow-up, which includes around a quarter of all scans. Most nodules are benign – hence the very high false positive rate. Many considered this approach over-cautious. UKLS took a different tack and delineated a second category in addition to false positives: the 'interval imaging rate' refers to those participants who ultimately did not have lung cancer but required only further follow-up imaging. By making this separation providers have a better understanding of the potential harms, but also the degree and type of follow-up, including the re-imaging burden. [9]

LCS proponents have developed several pulmonary nodule management guidelines, intended to standardise management. Whilst there is some variation between the

guidelines, a likely further explanation for the variation in false positive rates is their inconsistent application. When used appropriately, guidelines have been shown to decrease false positive rates, [10] and sensitivity and specificity have been further improved by incorporating semi-automated volumetry calculations (as opposed to diameter) and nodule risk scoring (e.g. the Brock Score). [11] The adherence of reporting radiologists to nodule management protocols is likely to be higher if part of a formal LCS study or programme, as opposed to when they are providing a routine clinical service. This may explain the high rates of false positive results being reported by screening services in the USA, where newly developed protocols were retrospectively applied and subsequently demonstrated a substantial reduction in false positive results. [12]

Overdiagnosis

Overdiagnosis refers to a cancer which is detected through screening that would not have caused symptoms or harm within a person's lifetime, had they not had the screening test. Variations in how to define, calculate and interpret overdiagnosis make translation to clinical practice challenging. As with "false positives", the rate of overdiagnosis depends on what we consider an overdiagnosed "cancer" to be. A key consideration is that all current definitions do not account for the clinical characteristics of the lung cancer, i.e. how aggressive the tumour is. [13] For example, many studies have shown that subsolid nodules present a higher risk of overdiagnosis as, if cancer, they tend to be indolent adenocarcinomas that can be safely monitored for growth, an approach which would only resect a lesion that has shown clinical progression[14–18]. In addition to how overdiagnosis is calculated, the impact it has on the individual varies substantially by age and co-morbidities, [19] thus a 'one size fits all' approach for both patients and nodule types does not work. A recent meta-analysis by Durham et al reports the overdiagnosis rate to be 20%. [20] However, reported rates from individual randomised controlled trials with extended follow up suggest more favourable rates. The NLST found that at 4.5 years follow up after the last screen, the overdiagnosis rate was 18%; [21] however, with extended follow up to a median of 12.3 years, it reduced to 3%. [22] A similar trend was seen in the NELSON study, which reported an overdiagnosis rate of 19.7% at 10 years, reducing to 8.9% at 11 years follow up. [8] Whilst these rates are promising, Callister et al. report that these RCT findings are likely to represent an underestimate of the problem, due to those participating in research studies not being representative of the age and fitness of a real world population. [19] This highlights the need for ongoing work not only to define overdiagnosis in an LCS setting, but also understand the true impact in a real-world setting. Despite this uncertainty, no authors suggest it should be a barrier to screening, rather an opportunity to further refine patient selection to optimise the benefit-harm ratio.

Psychological distress

Considering psychological impact is particularly pertinent for LDCT screening where false positive results, overdiagnosis and detection of incidental findings in

asymptomatic people, all have the potential to cause distress. Short-term adverse psychological burden has been reported, particularly after a false positive result, but this was found to diminish over time. [23,24] Importantly, the UKLS team found that the short term increase in cancer distress score did not reach a clinically significant level. [24] However, the evidence base is small and outcome measures between studies vary suggesting further research would be beneficial. A recent UK study placed emphasis on evidence-based, patient-centred communication and psychological preparation for different types of outcome, all of which are feasible to implement in a screening programme. It was found that doing this may reduce negative experience, however, further research would be required to confirm this. [25]

Targeted Screening and Risk Stratification

Appropriate risk stratification optimises the benefit-harm ratio of LCS and is therefore key for successful implementation. [26,27] However, how the target population should be defined, identified and invited is open for discussion. Initial rates of uptake in the US were as low as 1.9% of eligible individuals being screened, [28] only increasing to around 16.3% in some states by 2017. [29] Whilst many North American studies recruited participants using adverts, some European studies have moved towards a more tailored approach using population registries to contact individuals within the desired age range. [8,30,31] The French DEPISCAN study reported recruitment challenges when recruiting via primary care; [32] however, some UK studies have successfully taken advantage of the relatively comprehensive registration of UK residents with a primary care physician, enabling invitation based on age and smoking history. [33–35] Using this approach has seen substantially higher rates of uptake to the screening offer, including 52.6% seen in the Lung Screen Uptake Trial (LSUT), which also used bespoke targeted invitation materials. [34] On a larger scale, this approach would allow for true targeted population screening, with the option to account for other factors such as co-morbidities, in line with recent recommendations from Van der Aalst et al. in improving the uptake of those most at risk of lung cancer. [27] Pilot services are also investigating the ability of mobile scanners compared to hospital sites to widen access and optimise uptake of the screening invitation [33,35,36].

NLST screened participants based on two factors, age and smoking history. NELSON and USPSTF employ similar 'NLST-like' criteria; however, several validated models incorporating additional risk factors such as the Prostate, Lung, Colorectal and Ovarian ($PLCO_{m2012}$) model and Liverpool Lung Project (LLP) are available. Risk prediction models have been shown to be superior in selecting individuals for LCS compared to selection based on age and smoking history alone. [37,38] In particular, $PLCO_{m2012}$ has demonstrated increased sensitivity and efficiency in identifying who to screen, when compared with NLST. [39] It is important to consider that the performance of individual risk stratification models will vary between populations, as shown in the West London pilot study where LLP_{v2} was more permissive than $PLCO_{m2012}$. [35] Another important consideration is the limited recruitment to studies of those at the highest risk. As work continues to engage these individuals in LCS, further knowledge on risk stratification will be enabled. As always, it is worth remembering that risk models are not a panacea- even with the best risk prediction tools, a not insignificant proportion of

patients who ultimately develop lung cancer are ineligible for screening regardless of the criteria used. [40]

Radiation and cancer risk

A key concern for public health officials and screening bodies alike is the radiation that otherwise healthy screening participants will be exposed to using LDCT. For a chest scan to be considered 'low-dose', it should be 2 millisieverts (mSv) or lower, compared to a 'standard' lung CT dose of approximately 8 mSv. Scans are considered "ultra-low-dose" if they are less than 1 mSv; however, these definitions are the subject of debate. [41] More scans can be performed to meet so-called "low" or "ultra-low" dose standards, thanks to improved CT technology, meaning individual scan dose is kept acceptably low. There is, however, a strong argument for extra caution in the context of smokers and ex-smokers (the target demographic for LCS), as pre-existing lung damage places them at higher risk of lung cancer induction from radiation due to radiation and smoking damage interacting synergistically [42]. While a one-off LDCT confers a negligible increased risk of lung cancer, annual screening from 50-75 years of age, may confer an additional 5% risk for women and 1.5% for men [42]. One option to decrease the cumulative radiation dose for those undergoing long-term screening may be biennial scans[43,44], however, most existing data on efficacy and safety relate to annual programmes and extrapolating to biennial screening may be difficult.

When assessing the risk posed by radiation exposure, we must consider whether the benefit of identifying and curing lung cancer in this population outweighs the risk of causing cancers using LDCT screening. Rampinelli et al concluded that only 1 radiation-induced cancer could be expected for every 108 lung cancers detected in 10 years of annual screening. [45] So, while induced cancer rates are not negligible, they may be greatly outweighed by the ability of screening to find more early-stage lung cancers that can be treated.

Incidental findings

In contrast to screening tests for other cancers, LDCT has the potential to identify many other abnormalities in addition to lung cancer, known as incidental findings. The harms and benefits of identifying these have not, to date, been well explored. A 2008 systemic review, found the reported rate of incidental findings to be between 7-27%, which to many seem unacceptably high. [1,46] Incidental findings could, however, pose an additional benefit of LDCT screening, in the early detection of underlying disease, enabling prevention and treatment. Smoking-associated co-morbidities such as cardiovascular disease are common in this population and often go undiagnosed until a disease-specific event occurs. The presence of findings such as coronary artery calcification (CAC) may act as effective radiological markers to improve clinical outcomes from these co-morbidities. Data as to the utility of detecting incidental findings are mixed, and further confused by varying definitions of what constitutes a relevant finding and a lack of data on clinical outcomes of interventions. In 2007, the NELSON study demonstrated a negligible benefit of identifying potentially malignant

non-lung incidental findings on LDCT. It found only 1% of those in the LDCT arm had incidental findings with significant clinical implications, with no lives saved as a result of identifying them. [47] On the basis of this, they advised against systematically searching for incidental findings in LCS. However, this study categorised several findings including coronary artery calcification as 'not clinically relevant' and therefore outcomes from such findings were not assessed or reported within this study. In contrast, in 2012 the same group published new data which demonstrated that CAC scores were an independent predictor of all-cause mortality and cardiovascular events, [48] suggesting a potential clinical benefit, but reporting that further work would be needed before any change to their original guidance. Further to this, reporting of CAC has since been demonstrated to increase statin prescribing within a lung cancer screening population[49]. Whilst the exact prognostic benefit of CAC detection remains unclear particularly in a population who likely already qualify for primary prevention[50], 2016 guidelines now mandate radiologists to report CAC detected on LDCT[51] and European guidelines suggest the incorporation of CAC into risk assessment may be useful in those with a lower (5-10%) lifetime risk of cardiovascular disease. Unfortunately, much of the data around clinical utility of detection of other common incidental findings in LCS has even less evidence to support one approach over another. Individual nations will need to utilise the available evidence and adapt local protocols for investigation and diagnosis of incidental findings. An example of this includes the incidental findings management protocol for the UK based SUMMIT study, produced to report only those abnormalities that could lead to an evidence based intervention and meanwhile reduce burden on primary care physicians. [52] We summarise the current evidence for management of incidental findings in Table 1.

Cost effectiveness

A remaining question for many, not least policy makers, is will LCS be cost effective in the long term? There has, to date, been no published cost of a national screening programme. The infrastructure and workforce required to run such a programme is significant, including the provision of CT scanners, clinic space, IT systems and staff. Not only should the impact of the screening test itself be considered but the downstream consequences of abnormal results and the additional impact this will have on existing services. Results from the UK-based UKLS and Manchester lung health check programme demonstrate favourable Incremental Cost-Effectiveness Ratios (ICER) of £8466 and £10,069 per Quality Adjusted Life Year (QALY) respectively. [31,53] These estimates were for one-off screens only, but they are substantially lower when compared to the NLST estimate of $81,000/QALY, [54] and lower than current estimates of UK breast cancer screening ICER, [55] and comfortably under the National Institute for Clinical Excellence (NICE) threshold of £20,000 - £30,000/QALY. [56]

Discussion

There is clear evidence demonstrating the effectiveness of LCS in reducing lung cancer mortality, which provides a route to improving the currently poor outcomes for those

with lung cancer. Despite this, perceived barriers to the implementation of LCS remain, providing potential reasons why European nations, still do not have co-ordinated screening programmes for lung cancer. Given the weight of evidence for the potential benefits of LCS, should these barriers continue to prevent the implementation of targeted LCS?

Until recently, the evidence base for LCS largely came from the US, causing concerns among some as to how translatable results would be to a non-US population. The reality was always that the health benefits were likely to be the same but the costs lower. Evidence from the NELSON study, and UK-based trials [31,33,57] and services, including the SUMMIT Study, the Yorkshire Lung Screening Trial, and the NHS England Lung Health check pilots, will continue to refine our understanding of how to implement LCS in Europe.

Some argue that the NLST mortality data is only the tip of the (beneficial) iceberg; the study was stopped a year early because the results in the LDCT arm were so impressive, results that would likely have improved further if more cancers were picked up in future screening rounds, as they would be in an implemented screening programme rather than a 'stop screening design' trial. In addition, those recruited to NLST were typically at lower risk of lung cancer than those expected to be eligible for LCS in the general population due to bias in recruitment. It therefore potentially underestimates the impact with a programme reaching those at the highest risk could have.

In 2017, a European group of LCS experts produced the European position statement on LCS, largely in support, but also acknowledging some of the barriers discussed in this article. [58] Their recommendations include the use of validated risk stratification models (above age and smoking history alone) and standardised, evidence-based nodule management guidelines, both of which reduce false positive results. No single risk stratification model has been shown to be superior in a given population; however, a pragmatic approach would be to select one or more, accepting an iterative refinement process as further evidence becomes available to optimise screening efficiency and cost effectiveness. It also advocates for unified and adequate quality assurance programmes to ensure that standards are met for risk stratification processes, radiological reporting and follow-up intervals, to facilitate a standardised approach and future improvements.

The potential harms of LCS are important considerations and should not be dismissed; however, as LCS evidence and experience has increased, initial concerns appear less serious. Some areas require ongoing work. An example of this includes understanding the potential benefits or indeed extent of harm that could be caused from identifying incidental findings in LCS. Whilst this important work continues, the uncertainty around incidental findings should not prevent screening for lung cancer. Proposed pragmatic approaches to only report abnormalities for which there is an evidence base for the diagnosis, investigation and management, seem reasonable and are being utilised in practice. Discussion of potential harms should be included in the shared decision-making process for screening participation, with a balanced summary

provided. Whilst any individual is entitled to take the personal decision not to participate based on these, none should be a barrier to screening at a population level. And while further data is certainly needed to refine the LCS paradigm, this need should not be a barrier to implementing screening and starting to change cancer outcomes now.

Conclusion

Lung cancer is the single deadliest cancer in the world. LDCT screening identifies early lung cancers, when they can be cured, and has been shown to significantly reduce lung cancer mortality by at least 20%, with early evidence to demonstrate its cost effectiveness. Despite this, few truly population-based screening programmes exists in Europe. Elements of the screening pathway would benefit from further refinement; however, feasible, evidence-based solutions exist to enable implementation on the understanding that these could be iteratively improved. The potential harms of LDCT screening must always be considered and discussed with those participating, but with the passage of time, studies have found many of these harms to be less of a concern than previously thought. For those risks which remain, appropriate, acceptable mitigations are available, suggesting that none should serve as barriers to the implementation of national, unified LCS programmes across Europe and beyond.

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Table 1. Evidence base for managing incidental findings detected at CT screening.
NICE: National Institute of Clinical Excellence, **ACR:** American College of Radiologists, **ELCAP:** Early Lung Cancer Action Project, **SCCT/STR:** The Society of Cardiovascular Computed Tomography/Society of Thoracic Radiology.

Condition	European Evidence	US evidence
Abdominal aortic dilatation	NICE [1] <3cm: No action required. ≥3cm <5cm**:** Refer to local vascular team for surveillance. ≥5cm: Urgent referral to local vascular team for assessment.	
Adrenal opacities	European Society of Endocrinology [2,3] 1< and <4cm, plus <10 Hounsfield Units (HU): Excess cortisol and catecholamine investigation. If no excess hormone, no further action. >10HU or >4cm: Endocrine MDT referral	American College of Radiology (ACR) [4] <1cm or <10HU: No action required. >1cm and <2cm: 12 month follow up CT 2cm≤ and <4cm: Adrenal CT, if <10HU no further follow up, if >10HU adrenal washout CT ≥ 4cm: Endocrine MDT assessment – consider resection if no previous cancer, consider biopsy +/- PET if previous cancer
Anterior mediastinal mass (suspected thymoma)		ACR [5] Cystic AND anterior or middle mediastinal compartment: No further follow up Non-cystic AND anterior or middle mediastinal compartment: MRI +/- PET scan via respiratory clinic Posterior: MRI via respiratory clinic
	Other evidence: ELCAP Lung Cancer Screening – masses <3cm remained stable. [6] Framingham Heart Study >20% growth in 6 of 8 masses <3cm. [7]	
Ascending thoracic aortic dilatation		ACR [5] <4cm: No further action required. ≥4cm <5.5cm: Non-urgent referral to cardiology team. ≥5.5cm: Urgent referral to local cardiothoracic team.
Interstitial lung disease		Fleischer [8] Non-dependent abnormalities involving at least 5% of a lung zone: Clinical review and spirometry with respiratory evaluation if suggestive of ILD. Interval re-assessment in patients with clinical or radiological risk factors and normal spirometry.

Thyroid nodules		ACR [9] ≥1.5cm, abnormal local lymph nodes, or invasion of local tissues: outpatient ultrasound scan of neck.
Coronary Artery Calcification (CAC)	European Guidelines on Cardiovascular Prevention [10] Report CAC to primary care physician where CAC where Qrisk2 5-10%	SCCT/STR [11] Report all CAC to primary care physicians
	Other evidence: Jacobs et al 2012 sub cohort of NELSON participants found CAC is independent predictor of all-cause mortality and cardiovascular events. [12] Tailor et al 2021 found statin prescription improved in patients after CAC reporting even in patient who already met prescription criteria prior to CAC report. [13] Ruparel et al 2019 Evaluation of cardiovascular risk in Lung cancer Screening found 98% have QRISK>10%. [14]	
Osteoporotic (wedge) vertebral fracture(s)	Royal Orthopaedic Society Guidelines [15] Refer for DEXA or to metabolic bone clinic	
	Other evidence: De Jong et al 2014 - Nelson sub-study suggests high burden of vertebral wedge fractures in LCS population, particularly in current smokers. [16]	

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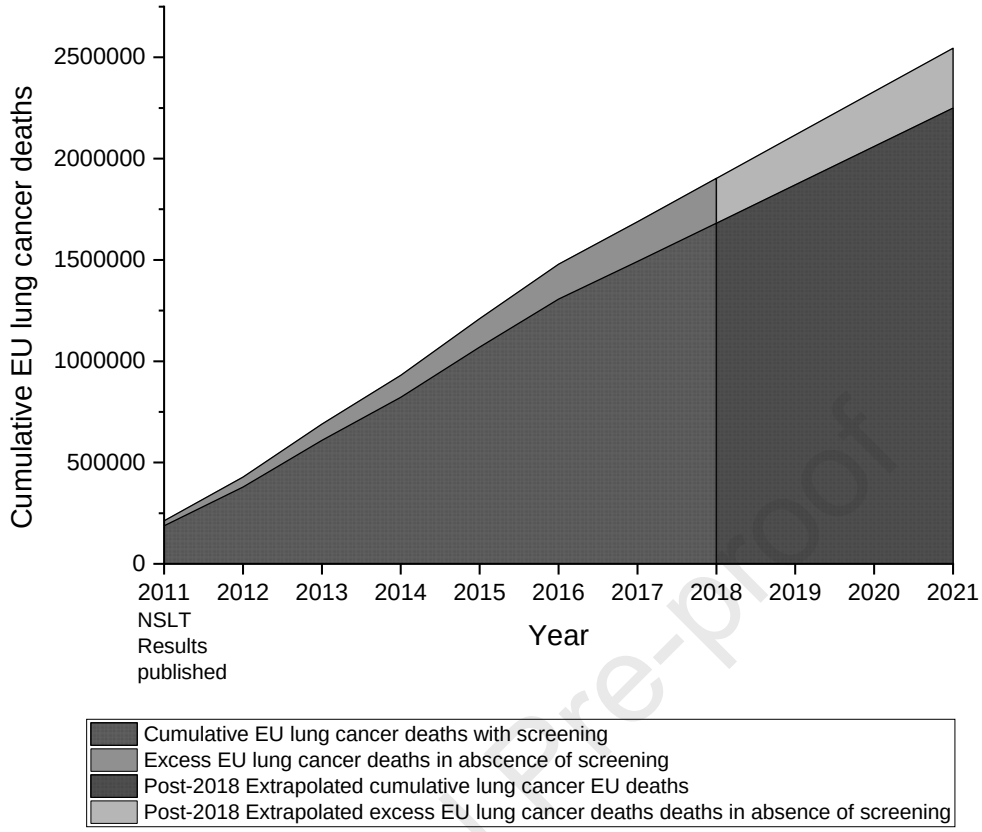

Figure 1: LDCT screening – a decade of delay.

Cumulative lung cancer mortality for European Union countries from 2011 to 2021 including 295,175 potentially preventable deaths if lung cancer screening had been implemented. Mortality data derived from WHO Mortality Database up to 2018. [1]

2018 to 2021 yearly mortality estimated from average yearly EU mortality from 2011 to 2018. Estimated 58% of lung cancer patients across Europe would have been met USPSTF criteria for screening in 55- to 80-year-olds. [2] Relative reduction in mortality of 20% from NSLT. [3]

NSLT: National Lung Screening Trial, USPSTF: United States Preventative Services Task Force.

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