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How will lung cancer screening and lung nodule management change the diagnostic and surgical lung cancer landscape?

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Lung cancer screening implementation and subsequent findings management will change the lung cancer landscape. <https://bit.ly/3W8xPCA>

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Abstract

Introduction: Implementation of lung cancer screening, with its subsequent findings, is anticipated to change the current diagnostic and surgical lung cancer landscape. This review aimed to identify and present the most updated expert opinion and discuss relevant evidence regarding the impact of lung cancer screening and lung nodule management on the diagnostic and surgical landscape of lung cancer, as well as summarise points for clinical practice.

Methods: This article is based on relevant lectures and talks delivered during the European Society of Thoracic Surgeons–European Respiratory Society Collaborative Course on Thoracic Oncology (February 2023). Original lectures and talks and their relevant references were included. An additional literature search was conducted and peer-reviewed studies in English (December 2022 to June 2023) from the PubMed/Medline databases were evaluated with regards to immediate affinity of the published papers to the original talks presented at the course. An updated literature search was conducted (June 2023 to December 2023) to ensure that updated literature is included within this article.

Results: Lung cancer screening suspicious findings are expected to increase the number of diagnostic investigations required therefore impacting on current capacity and resources. Healthcare systems already face a shortage of imaging and diagnostic slots and they are also challenged by the shortage of interventional radiologists. Thoracic surgery will be impacted by the wider lung cancer screening implementation with increased volume and earlier stages of lung cancer. Nonsuspicious findings reported at lung cancer screening will need attention and subsequent referrals where required to ensure participants are appropriately diagnosed and managed and that they are not lost within healthcare systems.

Conclusions: Implementation of lung cancer screening requires appropriate mapping of existing resources and infrastructure to ensure a tailored restructuring strategy to ensure that healthcare systems can meet the new needs.

Introduction

Lung cancer is the most frequent type of malignancy and the leading cause of cancer-related deaths worldwide [1–3]. The majority of lung cancer cases are diagnosed at an advanced stage, where radical treatment is not an option [3]. Lung cancer screening for high-risk populations with low-dose computed tomography (LDCT) is a valid intervention to increase lung cancer diagnosis at an early stage, where radical treatment can be offered and reduce lung cancer mortality [4–10]. However, systematic implementation of LDCT lung cancer screening requires a robust system and process to ensure that



uncertainties are addressed and all relevant findings are managed appropriately. Almost 50% of lung cancer screening LDCTs will report a lung nodule and only 5% of those will be malignant [10, 11]. The detection of lung nodules during lung cancer screening triggers a new diagnostic and treatment pathway that frames a new landscape in the multidisciplinary management of abnormal findings. This article is based on relevant lectures and talks delivered during the successful European Society of Thoracic Surgeons (ESTS)–European Respiratory Society (ERS) Collaborative Course on Thoracic Oncology held in Zurich (Switzerland) in February 2023. Due to the fast-changing field we additionally performed a literature search until December 2023 to ensure we captured recent data. This article aims to present the most updated expert opinion, discuss relevant evidence and further our understanding of the impact of lung cancer screening and lung nodule management on the diagnostic and surgical landscape of lung cancer.

Search strategy

Original lectures and talks addressing the subject from the ESTS-ERS Collaborative Course on Thoracic Oncology and their relevant references were included. An additional search including the words or variations of “lung nodule”, “diagnosis”, “lung cancer screening” and “thoracic surgery” was conducted, and peer-reviewed studies in English from December 2022 to June 2023 from the PubMed and Medline databases were evaluated with regards to immediate affinity of the published papers to the original talks presented at the course. Letters to the editor, congress abstracts and case reports were excluded. An additional search with the same criteria was conducted from June 2023 to December 2023 to ensure that all latest literature is captured in the rapidly evolving field of lung cancer screening.

Lung cancer screening in Europe: different gears in various countries

Currently, three European countries run national lung cancer screening programmes (Croatia, Czech Republic, Poland) while the rest run clinical trials and/or implementation studies (table 1). National lung cancer screening programmes in Europe share similarities in the use of quantified inclusion criteria (age and smoking habit cut-offs) rather than risk stratification models. Age as a lung cancer screening inclusion

TABLE 1 Current lung cancer screening situation in various European countries

	National programmes	Implementation studies	Clinical trials
Albania	0	0	0
Austria	0	0	0
Belgium	0	0	1
Bosnia and Herzegovina	0	0	0
Bulgaria	0	0	0
Croatia	1	0	0
Czech Republic	1	1	0
Denmark	0	0	1
Estonia	0	1	0
Finland	0	0	0
France	0	15	0
Germany	0	2	1
Greece	0	0	0
Hungary	0	2	0
Italy	0	9	2
Kosovo	0	0	0
Latvia	0	0	0
Lithuania	0	0	0
The Netherlands	0	2	1
Norway	0	0	0
Poland	1	3	0
Romania	0	0	0
Serbia	0	1	0
Slovakia	0	0	0
Slovenia	0	0	0
Spain	0	6	0
Sweden	0	1	0
Switzerland	0	1	0
United Kingdom	0	16	3
Information from [12].			

criterion is 50–75 years in Croatia, 55–74 years in the Czech Republic and 50–74 years in Poland. Quantification of smoking habit as an inclusion criterion is ≥ 30 pack-years in Croatia and ≥ 20 pack-years for Poland for current smokers. In Croatia and Poland, ex-smokers are included up to 15 years after quitting. These national lung cancer screening programmes vary in their duration and funding sources [13–15]. Information on recruitment strategies per country is not readily available from the relevant lung cancer screening websites, and a thorough literature search is required to obtain access to detailed information. To date, none of these programmes have publicised specific information on the invitation process, standard operating procedures and obstacles. Another common theme across all countries is the importance of engaging primary healthcare in the recruitment of high-risk individuals who could benefit from lung cancer screening. Ensuring the engagement of family physicians and general practitioners (GPs) remains a significant challenge around Europe and providing training to GPs in lung cancer screening has been recognised as a priority [16, 17].

High-risk individuals around Europe have variable access to lung cancer screening depending on its availability in each country. Variable access implies heterogeneity in processes, structure, quality and provision of service. To address this, the European Society of Radiology and the ERS recommended lung cancer screening in comprehensive, quality-assured, longitudinal programmes within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres [18]. The need for clear algorithms in radiology reporting and further management of findings remained. This has been recently addressed through a technical standard report for a comprehensive high-quality lung cancer screening programme [19] and, in a joint effort, a statement on management of incidental findings from LDCT screening for lung cancer [20]. The management of these findings requires a systematic multidisciplinary approach [21]. In contrast to other cancer screening programmes, LDCT provides much more information than required for lung cancer detection [20]. Incidental findings are detected frequently, and they can potentially trigger further investigations that may benefit or harm the participants while increasing management costs [22–25].

Despite the existing variation of healthcare systems across European countries and their differences in comparison with countries outside Europe, it seems that the national lung cancer screening programmes in Europe share similar underpinning principles with the national lung cancer screening programmes in the United States of America, South Korea and Taiwan [26–31].

The need for clear algorithms in radiology reporting and further management of findings is a common theme which has been addressed in the United States, South Korea and Taiwan through the adoption and implementation of the Lung Imaging Reporting and Data System (Lung-RADS) protocol (<https://acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads>). This ensures a systematic approach therefore minimising confusing variation in practice and potential serious incidents.

Similarly to Europe, primary care is a key stakeholder in national lung cancer screening programmes outside Europe, being a main source of identification and referral of high-risk individuals for lung cancer screening [26–31]. Each country adopts the applicability based on existing resources and infrastructure, but they all share similar underpinning principles [32].

Impact on lung cancer services of suspicious findings upon lung cancer screening

Translating lung cancer screening research to real-world programmes has multiple, different challenges across various global healthcare systems [33]. Lung cancer screening impacts on care pathways, in particular clinic appointments and capacity, downstream investigations and interventions towards lung cancer workup, pulmonary function testing (PFT), smoking cessation and costs.

Impact on clinic appointments and capacity

Current lung cancer services are inundated; therefore, the implementation of lung cancer screening requires comprehensive planning within relevant healthcare systems as well as involvement of professional organisations to ensure the successful delivery of lung cancer screening programmes. Assessing and planning the health infrastructure capacity for the resources required is needed in advance to ensure that implementation is feasible [33, 34]. Staffing levels, infrastructure, resources and capacity need to be primarily addressed and they should be complemented by governance, quality assurance and programme outcome reporting protocols [33]. Accreditation of screening centres with incorporation of multidisciplinary teams (MDTs) [21] and access to fast-track lung cancer clinical services needs to be in place with a quick turnaround time for diagnostics.

Geography and impaired infrastructure in rural and remote locations may represent a challenge to lung cancer screening provision when compared to urban populations. There is a certain bias towards urban-centric health promotion strategies, which are less effective in rural areas [35].

In these cases, mobile LDCT units have demonstrated potential by reducing travel and improving access to a screening programme outside of a traditional hospital setting which is already overwhelmed by existing clinical services [33]. This method was successfully used for lung cancer screening in rural areas in Japan in the 1990s [36] and its current use in high-risk populations in the United Kingdom and United States continues to expand [37]. Efforts such as the mobile LDCT units appear to be a feasible and acceptable strategy to increase capacity in overstretched radiology departments.

Implementation of a lung cancer screening programme will result in a significant tumour-stage shift, leading to increased workload for thoracic tumour MDTs and theatres, requiring workforce and capacity planning [26]. If curative treatments for screen-detected lung cancers cannot be provided in a timely manner due to lack of capacity, then lung cancer screening cannot benefit the participants [33]. Therefore, treatment capacity will need adaptation over time to meet the increasing demand. Available data suggest that modelling can be utilised in the development of a screening programme by predicting the future clinical problem, assessing the potential impact of different interventions and capacity planning for screening implementation [33, 34, 38, 39]. By these measures, inequalities in access to multidisciplinary lung cancer services may be ameliorated [40].

Impact on imaging and sampling investigations

If the LDCT screening outcome is suggestive of lung cancer or other suspicious findings, an urgent secondary care referral will be required [21]. In the case of suspicious findings for lung cancer, further investigations follow, including positron emission tomography (PET)/computed tomography (CT), bronchoscopy with endobronchial or transbronchial biopsy, endobronchial ultrasound (EBUS) with transbronchial needle aspiration/biopsy and CT-guided biopsy [41, 42].

These investigations are already in high demand within the existing lung cancer services; therefore, the addition of lung cancer screening participants will further increase waiting times. Decreasing the examination time by using advanced devices is a way to investigate more patients within the same timeframe. The new generation of total-body PET/CT scanners with a long-axial field-of-view offer increased lesion detectability, reduced acquisition time and/or reduced administered dose [43]. These characteristics led to reduced overall time for a single scan, thus allowing a higher number of studies as compared with former generations of PET/CT scanners [44]. The higher number of studies will subsequently increase the workload of nuclear medicine specialists and radiologists in reporting. Suspicious findings will be discussed during thoracic tumour MDT meetings [21] and further investigations will be required for tissue sampling. This can lead to increased referrals to bronchoscopy units for bronchoscopy/EBUS. For those lesions not accessible *via* the endobronchial route, CT-guided transthoracic biopsy demonstrates an alternative approach [45–47]. With the existing shortage of interventional radiologists, significant delays will be anticipated [48, 49].

Impact on PFTs

PFT is part of the respiratory basic workup delivering functional insight (obstructive or restrictive). Several parameters, such as forced expiratory volume in 1 s or the diffusion capacity of the lung for carbon monoxide, are taken into account when a patient is discussed for thoracic surgery [50]. During the anticipated shift from advanced to early lung cancer stages, the number of PFTs is expected to rise. However, PFT is not necessarily bound to lung cancer service. PFT can be decentralised to outpatient clinics.

Impact on smoking cessation services

Lung cancer screening and smoking cessation follow a *conditio sine qua non* formula. According to international guidelines and statements, smoking cessation should be integrated in lung cancer screening programmes [16, 18–20, 35, 36, 51]. Geography affects access to smoking cessation services and management protocols may vary depending on the area. Lung cancer screening programmes will presumably increase the number of individuals wishing to quit smoking; hence, an additional smoking cessation infrastructure will be required.

Costs

In 2014, the United Nations reinforced its political commitment to implement a national and global roadmap towards effective prevention and control of noncommunicable chronic diseases [16]. The main priority is the goal of a 25% relative reduction in overall mortality from noncommunicable chronic

diseases, including cancer. Because most countries struggle with budget and sustainability constraints regarding their national health systems, it is crucial that the most cost-effective health interventions are prioritised, both at the individual and population level [16].

The management of incidental findings detected during lung cancer screening is likely to be a key factor in overall effectiveness and cost-effectiveness of the programme [20].

Data support the notion that lung cancer screening together with smoking cessation efforts can be cost-effective as a population-based measure [39]. With focus on low- and middle-income countries, effectiveness, affordability, feasibility and cost-effectiveness of LDCT screening vary among them due to differences in lung cancer epidemiological patterns and the readiness of their healthcare systems, resulting in a need for country-specific analyses [52, 53].

Region- or country-specific cost-effective analysis would be necessary to estimate individual expenditures. An important question remains unanswered: will lung cancer screening be funded by the community or individually? The answer will impact the number of potential participants in lung cancer screening.

Impact of lung cancer screening with nonsuspicious findings on services

Unlike other screening programmes, lung cancer screening using LDCT encompasses multiple organ systems, making it more complex, but also more interesting, as it may identify multiple abnormalities. In nearly 70% of cases, thoracic and extrathoracic incidental findings unrelated to lung cancer have been reported [23, 54]. Many may not have clinical significance and should not affect the screening process [55, 56]. However, there are significant incidental findings that influence patient prognosis and may call for specific actions [57].

The incidence of incidental findings varies depending on the age and origin of the screened population, the prevalence of active smoking and, most importantly, the significance highlighted by the radiology report. The variability of reporting incidental findings is very high, ranging from 28% in community imaging centres to 67% in university centres [58]. This variation imposes criticism on lung cancer screening reporting, but it is also seen as a significant opportunity for early detection of other pertinent diseases [59–61].

The definition of significant incidental findings and their clinical relevance has been a much-debated topic since screening programmes began. Initial data from the National Lung Screening Trial (NLST) and the Dutch–Belgian lung cancer screening trials (NELSON) have described a relatively low incidence of clinically relevant incidental findings (7.5% and 8.4%, respectively) [4, 56]. Despite this, experts insisted on the need to unify criteria and definitions. In 2014, the American College of Radiology (ACR) introduced the first version of Lung-RADS to recommend a standardisation in lung cancer screening reporting, including the “S” category to define clinically significant or potentially clinically significant incidental findings (<https://acr.org/Clinical-Resources/Reporting-and-Data-Systems/Lung-Rads>). Subsequently, several evidence-based white papers have been published that offer recommendations specific to each organ [62–68]. Recently, the ERS addressed the matter with a joint statement in collaboration with other scientific organisations [20].

According to the published evidence to date, coronary calcifications and emphysema are the most prevalent findings according to most studies [20, 62–68]; however, abnormalities in all organ systems visible on the LDCT are frequently reported.

Coronary artery calcification

Atherosclerotic cardiovascular disease (ASCVD) is a major cause of death, and the presence of coronary artery calcification (CAC) is a well-known specific marker for atherosclerosis. The most common approach to quantify this is the Agatston CAC score, which recognises lesions with an area ≥ 1 mm² and attenuation >130 HU [69]. The CAC score is clinically significant, as it predicts overall mortality and unfavourable cardiovascular events. When severe, coronary heart disease risk increases nine to 16 times [70, 71], whereas the absence of CAC (CAC=0) confers a very low risk of ASCVD, allowing for reclassification as lower risk, and even deferring specific treatment [72].

In lung cancer screening, the rate of CAC detection is high. Although it is frequently not recorded as a significant incidental finding, its prevalence ranges from 56% to 74% [23, 55, 73]. Cardiac CT and LDCT are technically different, but CAC is detectable and measurable by both, with excellent correlation. CAC evaluation with Agatston scoring or a simple visual assessment of LDCT enables the correct selection of

patients at higher risk of cardiovascular and all-cause mortality [74]. CAC is regularly not reported or underestimated during lung cancer screening, and patients who are mentioned or reported as a significant incidental finding are more likely to receive statin treatment for cardiovascular risk prevention (ORs 1.8 and 4.4, respectively). Depending on the structure of the healthcare system, CAC reporting at lung cancer screening triggers referrals to primary care and/or cardiology services for further investigations and management where required [75–77]. Specific lung cancer mortality is increased in subjects with CAC >400 independent of smoking and traditional risk factors [78]. Multiple large screening cohorts have demonstrated the prognosis impact of incidental CAC detection in LDCTs [79, 80].

In the most recent guidelines, cardiovascular societies in Europe and the United States formally endorse CAC as a strong ASCVD risk modifier and recommend it in specific scenarios. It is worth noting that CAC=0 has been explicitly addressed to reclassify risk downward and avoid statin therapy in some groups [81–84]. A large-scale asymptomatic population-based clinical trial (ROBINSICA) has already randomised 43 447 subjects to investigate whether CAC screening and preventive treatment is effective in reducing cardiovascular and all-cause mortality. Preliminary results show that 16.8% of women and 30.7% of men with a CAC score >100 urgently require preventive treatment [85].

The ROBINSICA trial [85] will answer many of the questions surrounding CAC detection during screening programmes and may potentially change current practice; meanwhile, with existing evidence the CAC score is reported in lung cancer screening LDCT reports. It can identify moderate-to-severe cases of cardiovascular risk, and it can reclassify this risk when a negative CAC (CAC=0) is reported, thus sparing unnecessary clinical appointments.

Emphysema

Emphysema is associated with an increased risk of lung cancer, independent of smoking. The presence of visually detected and automatically quantified emphysema are both linked with an elevated risk of lung cancer, with an overall pooled odds ratio of 2.3 (95% CI 2.0–2.6) [86]. A systematic literature review found the risk of lung cancer to be associated with centrilobular rather than paraseptal emphysema with a higher risk detected in moderate and severe emphysema (ORs 3.7 and 4.5, respectively). The quantification between mild, moderate and severe varies between the different studies, but most agree that the greater the amount of emphysema, the greater the risk [87].

The report of emphysema as an incidental finding in lung cancer screening varies and it depends on whether it is measured automatically using a cut-off value of –950 HU on noise-filtered LDCT or by visual assessment. The percentage low attenuation area used to detect and quantify emphysema has less interobserver variability than visual examination [88–90]. The ITALUNG cohort reported an emphysema prevalence of 32.3%, the SUMMIT cohort 33.4%, the NLST cohorts 45.4%, and the Cleveland Clinic cohort up to 50.6% [3, 23, 55, 91].

We consider it important to report the emphysematous changes as an incidental finding for two reasons. First, its presence is independently related to an increased lung cancer risk and it is a predictor of overall, lung-cancer-related and cardiovascular mortality in lung cancer screening participants [88, 91–93]. Second, emphysema is a highly sensitive and specific biomarker for COPD, and early detection, even if asymptomatic, could improve health status, by offering vaccinations to avoid exacerbations, encouraging regular exercise, managing comorbidities more proactively, and perhaps even starting medication to slow the pace of lung function loss. It is also known that subjects with asymptomatic undiagnosed COPD have an increased risk of pneumonia and exacerbations [94, 95]. Emphysema reporting will increase referrals to primary care/respiratory services and spirometry testing for quantification of lung function and will contribute to earlier diagnosis of COPD.

Other pulmonary incidental findings

Other lung incidental findings include bronchiectasis, interstitial lung abnormalities, tuberculosis and pleural findings such as pleural plaques/thickening and bilateral effusions [20].

Bronchiectasis is usually reported in 7.4–11.6% of patients during lung screening [3, 96]. In the International Early Lung Cancer Action Program cohort, this can reach up to 23% when specifically searched for by skilled radiologists. Bronchiectases are primarily located in the lower lobes, and those who have them experience a higher frequency of respiratory events and symptoms. Although it seems important to report them, bronchiectases are not usually considered a significant incidental finding, and further studies are needed to determine whether early detection could bring prognostic benefits [97, 98].

Interstitial lung abnormalities are incidental CT findings that affect >5% of a lung zone and are potentially compatible with interstitial lung disease (ILD). They include reticulations, ground-glass opacities, nonemphysematous cysts, honeycombing, parenchymal distortions and/or traction bronchiectasis. Interstitial lung abnormalities are classified into three categories: non-subpleural, subpleural nonfibrotic and subpleural fibrotic [99]. The prevalence in general population is 7%, and 2.5–7% in screening cohorts. Mortality risk in subjects with interstitial lung abnormalities detected during screening is increased, particularly for fibrotic interstitial lung abnormalities [93, 100, 101]. ILDs are frequent and potentially serious diseases that require an accurate diagnosis to offer treatments that modify their prognosis. For this reason, interstitial lung abnormalities should be considered as significant incidental findings and consequently reported in lung cancer screening, and patients should be subsequently referred to specialist clinics.

Osteopenia and osteoporosis

Treatment for osteoporosis or fragility fractures with osteopenia is strongly recommended, as it reduces fracture rates in real-world studies [102, 103]. Despite this, vertebral fractures and radiological findings suggesting osteopenia or osteoporosis are not usually reported as incidental findings in thoracic CTs [104]. In lung cancer screening subjects, the prevalence of vertebral fractures using the Genant semiquantitative method is 35%, and up to 51% in subjects who died during the screening period. Both vertebral fractures and bone density (measured in vertebral Hounsfield units) are independently associated with overall mortality [105]. The automatic measurement of Hounsfield units using artificial intelligence in LDCTs has demonstrated high diagnostic effectiveness for osteoporosis, and the fact that treatment for established osteoporosis reduces mortality suggests that an opportunistic screening of this condition could have a considerable impact [60, 106].

Referral implications

Opportunistic detection of non-lung-cancer-related conditions should bring health benefits to subjects and avoid unnecessary studies, stress and unjustified overcost. Certain significant incidental findings must be reported and generate specific action. Various studies have quantified the workload generated, numbering it between 11.2% and 15% of all screening cases. Most referrals and new diagnoses occurred after first-round screening and <1% required invasive procedures [73, 107].

Determining the clinical significance of incidental findings is a challenge, and a protocolised reporting approach is mandatory to identify relevant nondiagnosed comorbidities. Recently, GAREEN *et al.* [57] re-evaluated the negative screening LDCTs in the NLST and an expert panel classified the incidental findings in specific categories with a unique code. They found 8954 (33.8%) cases with a reported significant incidental finding, most of which were considered reportable to the referring clinician. Similarly, TISI *et al.* [55] published the SUMMIT protocolised incidental findings management protocol, which not only included specific assessment criteria, but also a suggested clinical action for each incidental finding. This approach generated referrals in 9% of screening subjects (5.1% to primary care, 1.1% for pulmonary consultation and 2.8% for cardiology/vascular). It is particularly noteworthy that while moderate, severe or very severe emphysema was described in 11.6% of cases, only 1.1% of cases were referred to a pulmonary consultation, although in all cases a spirometry was recommended.

From a patient-centred approach, two-thirds of lung cancer screening participants consider it very important to receive more information regarding respiratory and cardiovascular incidental findings. Despite 88% having understood the screening report, most prefer direct communication with clinicians, even when results are normal [108]. To minimise heterogeneity in the reports of incidental findings and their subsequent actions, the ACR has published a quick reference guide of incidental findings [109]. In 95% of cases, the lung cancer screening programme navigators found this useful or extremely useful [110].

It is currently unknown whether the reporting and action of incidental findings has a prognosis impact on screening subjects, but data suggest real potential benefits. More research efforts should be directed towards making use of lung cancer screening, and specific additional resources to address incidental findings should be considered.

The challenge of overdiagnosis

The concept of overdiagnosis in the context of lung cancer screening has been a matter of debate in the literature for more than two decades [111, 112]. It is important to consider the ongoing controversies related to overdiagnosis through the lens of critical appraisal of the data, taking into account the viewpoints of two diametrically opposed stances (the optimist, who promotes the benefits of lung cancer screening, *versus* the pessimist, who assumes the worst about it) [113, 114]. Given the complexity of this issue, much

discussion has focused on clarifying the meaning of overdiagnosis, ranging from a clinical perspective to an epidemiological definition, and finally, to one with a pathological basis that is commonly used today [111, 115, 116]. Moreover, the extent to which overdiagnosis occurs in the screening population, although widely explored, remains unclear, with variable estimates reported across different clinical trials and screening studies [4, 8, 9, 116–119]. Ascertaining the true magnitude of overdiagnosis in future lung cancer screening programmes remains a major hurdle, although modelling may help derive additional information to extrapolate beyond the time periods of the clinical trials [120]. Conducting research on overdiagnosis, with the aim of reducing its prevalence in order to mitigate any associated harms, is largely hampered by its retrospective nature; that is, it cannot be carried out prospectively, since direct observation in real time in an individual patient is not possible [121].

Definition of overdiagnosis

Many definitions of overdiagnosis exist in the literature. A consensus on a satisfactory interpretation of this term is essential to prevent and minimise misdiagnosis and overtreatment, with the aim of delivering more effective healthcare [122]. As pertains to cancer screening, a seemingly acceptable and commonly used meaning of overdiagnosis is the discovery of indolent pathology that would not have otherwise progressed to a clinically apparent illness and/or caused death during the lifetime of the individual [116, 123]. Essentially, otherwise asymptomatic people are unnecessarily but “correctly” diagnosed and classified as patients, then subsequently overinvestigated and overtreated, deriving little to no benefit from the diagnosis and treatment, and in the process are thereby harmed [122, 124, 125]. Regarded as the most severe potential harm of lung cancer screening, overdiagnosis has two major causes: overdetected (*i.e.* use of increasingly sensitive tests to identify indolent, nonprogressive or regressive abnormalities) and overdefinition (*i.e.* expanded definitions of disease with lowering of disease thresholds) [122, 125]. Other contributing factors to overdiagnosis have also been identified, such as fear of missing a diagnosis or malpractice suits, public enthusiasm for screening or testing and financial incentives [124, 125]. In addition, overdiagnosis in cancer screening occurs more frequently when there is slow or no growth of cancer pathology and/or high competing risk of death [16, 118].

Estimation of the degree of overdiagnosis of lung cancer in LDCT screening

The approach to quantifying overdiagnosis is based on a thorough analysis of data collected from long-term observation after screening ends [115, 126]. Research suggests that the magnitude of overdiagnosis at the population level is trivialised with extended post-screening follow-up periods [126]. For instance, overdiagnosis risk (probability that any lung cancer detected by LDCT is an overdiagnosis) was estimated at 18.5% initially (mean follow-up of 4.5 years) *versus* 3% ~9 years after last screen in the NLST [4, 127]. Estimations of the degree of overdiagnosis in the NELSON trial show a similar trend, with 19.7% *versus* 8.9% at 4.5 and 5.5 years after final screening, respectively [5]. However, the exact degree of overdiagnosis in cancer screening trials is unknown due a number of factors: inadequate trial design, varying definitions of overdiagnosis and different methods used to estimate extent of overdiagnosis [120, 128]. Furthermore, due to high risks of bias associated with many randomised trials, the true extent of overdiagnosis is probably underestimated [128]. Microstimulation models may be useful tools to provide more accurate estimates on overdiagnosis for lung cancer screening programmes with designs and populations that differ from those considered in the NLST and other screening trials [120].

Potential harms of overdiagnosis

The consequences of overdiagnosis can be subdivided into four main domains of harm (physical effects, psychological effects, financial strain and opportunity costs) based on a proposed taxonomy [129]. Other potential downsides of overdiagnosis include the negative effects of receiving a medical (disease) label, side-effects of and quality of life affected by unneeded tests or treatment, large financial burden at an individual and healthcare system level, wasted resources and overmedicalisation of society [124, 125]. The key problem with overdiagnosis is that it may lead to overtreatment, either unnecessary or overaggressive [112, 122]. It is, therefore, imperative to prevent, or at least reduce, overdiagnosis in lung cancer screening.

Potential strategies to reduce overdiagnosis

Potential strategies to avoid overdiagnosis, thereby minimising overinvestigation and overtreatment, are highlighted by KAUCZOR *et al.* [16] as follows: 1) individualised lung cancer risk calculations and models; 2) conservative nonsurgical management (active surveillance) for ground-glass nodules according to guidelines; 3) volumetry-based management of nodules (calculating volume-doubling time); and 4) biennial LDCT scans (*versus* annual screening) [16, 130–132]. Another important strategy is to develop protocol thresholds during the baseline round of lung cancer screening that define positive results and recommendations for additional workup, thus eliminating unnecessary diagnostic tests [133, 134].

The challenge of overinvestigation (overtesting or overutilisation)

Overinvestigation, also referred to as overtesting or overutilisation, is a growing problem for healthcare practitioners worldwide, given its link not only to overdiagnosis, but also other potential unintended harms, such as misdiagnosis, false positives and false negatives [122, 135]. Although not every instance of overuse leads to overdiagnosis, the risk of the latter is proportionate to the degree of the former [122]. Broadly speaking, overinvestigation consists of the needless medical tests (including diagnostic and screening tests) performed in both asymptomatic and symptomatic individuals, that are not medically necessary for proper clinical decision making or improving health outcomes, and in their absence would present few if any consequences to the patient [135, 136].

Overinvestigation

False positives are inevitable in screening. False positive rates in lung cancer screening can reach up to 13% and they are affected by a number of patient-specific and site-/radiologist-specific factors [137]. The false positive rate per screening round varies in lung cancer screening trials [138]. A significant concern with false positive results is that the use of finite healthcare resources (*i.e.* already overloaded lung cancer services) prevents their redistribution to patients with true positive results who would have benefited from tests, treatment and other interventions [135].

The mental health impacts of lung cancer screening, including psychological and social aspects, are largely unknown and not yet well understood [139, 140]. Existing evidence on the short- and long-term mental health effects of screening (including false positives and overdiagnosis) is limited [140]. Data in the literature support both the negative and positive effects of cancer screening on mental health [140]. The main issue with false positive results (indicating that the person possibly has the disease when they do not) in screening tests is the psychosocial toll they take on the recipient (*i.e.* generating stress and increasing anxiety, depression, post-traumatic stress disorder and suicide, as well as straining personal relationships) [138, 140, 141]. In the Danish Lung Cancer Screening Trial, an association between more negative short-term psychosocial consequences and false positives was found compared with the control group and true negatives [138]. In the NELSON trial, no negative effects were found in health-related quality of life (HRQoL) among 351 participants up to 6 months after CT scanning [142]; the only discomfort was reported in connection with having to wait for the results of the CT scan and dreading those results. At 2 years follow-up, the HRQoL of 733 screened subjects was similar to that of 733 control subjects; the unfavourable short-term effects of an indeterminate baseline screening result had resolved [143]. Quantification of the psychosocial effects of screening may be carried out using patient-reported outcome measures *via* self-reported questionnaires [139]. Clinicians can help alleviate patients' stress and improve adherence to screening by keeping them well-informed throughout the screening process and after receiving the results [139].

The need for artificial intelligence and imaging biomarkers to reduce false positives and unnecessary investigations

Artificial intelligence (AI), a term coined by John McCarthy in 1956, is the approach of using computers and technology to simulate human-like intelligent behaviour and critical thinking [144]. In LDCT screening for lung cancer, the application of AI in imaging diagnostics plays a key role in automatic nodule detection using a computer-aided detection system to reduce the burden of radiologists and identify lung structures suspected of malignancy [145, 146]. Effective nodule classification techniques, deep-learning application systems (*e.g.* convolutional neural networks) and radiomics can reduce false positive rates by increasing the sensitivity (accuracy) of screening and supporting the overall diagnosis and management of patients [146, 147]. Further advantages of integrating AI into lung cancer screening include reduction of radiation dose, enabling risk stratification and screening personalisation, and improving time to image interpretation [146]. In addition to AI, ongoing research points to the need for adjunctive testing using liquid biomarkers to complement imaging as a lung cancer screening tool to aid in early diagnosis of disease and risk prediction and decrease false positives [148]. Several biomarkers, such as autoantibodies and blood protein profiling, are currently available for clinical use, but many promising ones (*e.g.* autoantibodies, circulating tumour DNA, complement fragments, microRNA and DNA methylation) still require further validation studies [148]. The use of biomarkers in lung cancer screening will help optimise risk prediction models, improve diagnostic accuracy of indeterminate pulmonary nodules by enriching the screening population, and ultimately curtail the false positivity of LDCT scans and reduce the number of unnecessary referrals [148].

Impact of lung cancer screening on surgical approaches

Wide implementation of lung cancer screening is expected to increase early-stage lung cancer diagnosis by up to 70%, thereby shifting the stage distribution at the time of diagnosis [4–9]. Earlier lung cancer

stage is projected to increase the total lung cancer surgical volume and the proportion of lung-sparing surgery [149, 150]. Increased surgical volume will increase demand for theatre lists and thoracic surgery beds as well as pre-, peri- and post-operative care. Prolonged lung cancer screening implementation has also shown an upward trend in the incidence of carcinoma *in situ* and its precursor lesions, for which no robust management guidelines exist [149]. Despite the anticipated increasing trend in thoracic surgery volumes, the thoracic surgery workforce is projected to decrease, therefore creating a clear need for new post-surgical appointments [149, 151]. United States data predict a steady decrease of 25% in the number of practicing thoracic surgeons, from ~4000 surgeons in 2000 to ~3000 surgeons in 2050 [150]. Considering continued population growth and increasing life expectancy, the gap will widen further, resulting in the number of practising thoracic surgeons being half the number that is needed [152]. However, this gap is expected to narrow following long-term implementation of lung cancer screening programmes. Mathematical and simulation models have been applied in a Canadian lung cancer screening scenario and they considered lung cancer screening participation rate, clinical volume, retirement estimates and the number of new surgeons entering the workforce [153]. Following an initial increase, a subsequent fall in the surgical volume was predicted after the first 20 years of lung cancer screening implementation owing to a shift in the stages at diagnosis. Considering stages IA–IIIA as “operable lung cancer”, it has been forecast that the incidence of operable lung cancer per surgeon will reach 114 cases in 2030 [153]. Earlier stage at diagnosis in lung cancer screening participants that are asymptomatic and otherwise healthy will result in uneventful surgical resections with decreased hospital length of stay and subsequently increased income for the departments of thoracic surgery, as patients will stay fewer days than prognosticated by the insurance compensation policy, therefore utilising less hospital resources for the same compensation [154].

The technical challenge in early-stage lung cancer resection poses an important question for thoracic surgeons regarding the optimal surgical strategy to treat these patients. Minimally invasive access is preferred where applicable; however, there is an ongoing debate on whether a robotic approach is superior to video-assisted thoracic surgery (VATS) and whether the number of ports can affect clinical outcome (uniportal access *versus* two or three ports) [152, 154–156]. To date, there is no high-quality randomised controlled trial addressing the question of robotic surgery *versus* VATS for early-stage lung cancer, and no major survival or clinical benefit or difference in post-operative pain and recovery has been demonstrated between the various minimally invasive surgical approaches. A question that arises from the wider implementation of lung cancer screening programmes and their subsequent effect on surgical volume and caseload is what the impact of all this will be on thoracic surgery training overall.

Impact of lung cancer screening on oncological treatments

Lung cancer screening implementation is expected to offer a stage shift and diagnose up to 70% of cases in early-stage disease [4–9], which will impact on systemic and targeted treatments as well as immunotherapy offered in advanced-stage disease [157]. A recent cost-effectiveness analysis showed that earlier lung cancer diagnosis through lung cancer screening subsequently leads to reduced treatment costs. Lung cancer screening could potentially contribute to reducing the escalating costs associated with increasing cancer therapeutic related expenditures [158]. It can be assumed that stage shift at diagnosis will impact on the reduction of oncological workload relating to advanced stage patients and it will change the service delivery models in thoracic oncology to address the increasing needs of early-stage diagnosis. There is lack of real-world data to date regarding the financial and service impact of stage shift due to lung cancer screening. Following the implementation of national lung cancer screening programmes worldwide, it would be interesting for countries to share their data in this area and also present whether the stage shift at diagnosis has led to patient pathway review and redesign as well as to any changes in the delivery of healthcare models in thoracic oncology.

Lung cancer screening is anticipated to have an impact on the study landscape. Current research is mainly focused on therapeutic approaches for the treatment of advanced disease. However, implementation of lung cancer screening will result in a growing number of early-stage patients and a reducing number of advanced-stage patients. Clinical trials studying adjuvant and neoadjuvant treatment options at the early stage will become a priority and they will be even more meaningful in countries with national lung cancer screening programmes [159].

Table 2 summarises the impact of lung cancer screening on lung cancer services, services managing nonsuspicious findings, costs, overdiagnosis and overinvestigation, considerations for policies and procedures, as well as expert consensus advice.

TABLE 2 Succinct presentation of the impact of lung cancer screening on lung cancer and non-lung cancer services, costs, overdiagnosis and overinvestigation in combination with relevant considerations for the development of policies and procedures, as well as expert consensus advice

	Policy/process considerations	Expert consensus advice
Lung cancer clinic appointments and capacity	Advanced planning across the pathway Encounter distribution and geographic accessibility of the respective healthcare services to patients/participants	1) Prior to implementation, assess staffing levels, infrastructure, resources and capacity 2) Complement with governance, quality assurance and outcome-reporting protocols 3) Accreditation of lung cancer screening centres 4) Adaptation of treatment capacity over time to meet the increasing demand
Imaging/sampling investigations	Increased number of imaging and sampling investigations, which are already in high demand Consider infrastructure and trained personnel	1) Explore the option of advanced devices that will allow more patient scans within the same timeframe 2) Structured radiology reporting to ensure better use of radiology reporting time and decrease serious incidents 3) Plan in advance the training of interventional radiologists and pulmonologists, to ensure that increased biopsy demand is met
PFTs	Consider the potential increase in demand for PFTs	Decentralise in outpatient clinics
Smoking cessation services	Consider the increased demand in combination with geographical variation and access	Plan additional smoking cessation infrastructure
Costs	Consider the variation of effectiveness, affordability, feasibility and cost-effectiveness of LDCT screening among healthcare systems with different readiness	Country-specific cost-effectiveness data prior to implementation and service design
Services with nonsuspicious findings	Increased risk of overloading noncancer services without a clear operating procedure	Establish structured radiology reporting and patient care pathways for nonsuspicious findings, to ensure a streamlined process
Overdiagnosis	Overdiagnosis will utilise further resources	Set up a multidisciplinary diagnostic management team of experts (radiologists, pulmonologists, thoracic surgeons) to discuss and assess cases
Overinvestigation	Overinvestigation will utilise further resources	Set up a multidisciplinary diagnostic management team of experts (radiologists, pulmonologists, thoracic surgeons) to discuss and assess cases and consider the adjuvant use of artificial intelligence where available
Surgical procedures	Reallocation of theatre slots and review of presurgical assessments due to the early-stage shift at diagnosis	Thoracic surgery workforce to train and adopt minimally invasive techniques
Oncological treatments	Reduced workload in advanced-stage patients will affect service delivery and policies need to be updated accordingly	Restructure lung cancer services planning to ensure increased capacity for early-stage <i>versus</i> advanced-stage disease Develop research on early-stage lung cancer

PFTs: pulmonary function tests; LDCT: low-density computed tomography.

Conclusions

The wider implementation of lung cancer screening programmes is expected to change the landscape of lung cancer and healthcare professionals' perspective of managing the disease. Service capacity, infrastructure and resources need to be carefully studied on a regional and national level prior to wider lung cancer screening implementation. Furthermore, they should be adopted according to projected needs to ensure that lung cancer screening maximises its benefits without causing delays.

Points for clinical practice

- Careful service mapping is required prior to lung cancer screening implementation.
- Projected needs derived from lung cancer screening should guide service development and inform changes in infrastructure and resources.
- Lung cancer screening participant pathways should be organised on a national/regional level to ensure smooth navigation.
- Flow diagrams for the management of lung cancer screening findings are required to inform meaningful referrals and reduce overdiagnosis, as appropriate.

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