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Pulmonary nodules and CT screening: the past, present and future

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ABSTRACT

Lung cancer screening has come a long way since the early studies with chest X-ray. Advancing technology and progress in the processing of images have enabled low dose CT to be tried and tested, and evidence suggests its use can result in a significant mortality benefit. There are several issues that need refining in order to successfully implement screening in the UK and elsewhere. Some countries have started patchy implementation of screening and there is increased recognition that the appropriate management of pulmonary nodules is crucial to optimise benefits of early detection, while reducing harm caused by inappropriate medical intervention. This review summarises and differentiates the many recent guidelines on pulmonary nodule management, discusses screening activity in other countries and exposes the present barriers to implementation in the UK.

INTRODUCTION

Individuals diagnosed with lung cancer generally have a poor prognosis, largely attributable to delayed diagnosis due to the absence of discriminating symptoms at the early stages of the disease. In the UK, it was recently estimated for the period 2010–2012 that the net 5-year survival rate of lung cancer patients was 12.7%[1]—a reflection on the 67.6% of lung cancers that are diagnosed at stage III or IV.[2] One-year survival ranges from 14% for patients who present with stage IV disease to 71% for patients with stage I disease.[2] Early detection has the potential to transform lung cancer outcomes and the case for screening with low radiation dose CT (LDCT) has recently gained significant momentum. However, there is a need to ensure cost-effectiveness and minimisation of harms are considered in the face of a considerable healthcare burden that has arisen from these LDCT studies; namely the management of the pulmonary nodule. In this review, we briefly discuss the pedestrian history of lung cancer screening through to the rapid evolution of the present, and highlight potential important differences in the management of the pulmonary nodule between recent guidelines.

THE HISTORY OF LUNG CANCER SCREENING

Studies in screening for asymptomatic lung cancer began in the 1950s using photofluorograms. As early as 1959, it was clear that the lung cancer detection rate varied depending on whether medical risk was used to select the population to be screened.[3]

Early studies using chest X-ray

Unfortunately, the trials for chest X-ray (CXR) screening for lung cancer failed spectacularly. Four large randomised controlled trials in the 1970s–1980s[4–7] failed to detect a significant mortality benefit from CXR screening. Sadly, none of these studies used a true, null screening control group and rather compared screening with different modalities or at different frequencies. The Mayo clinic and Czechoslovakian studies compared CXR and sputum cytology at lower and higher frequencies.[4 7] Both the John Hopkins and Memorial Sloan Kettering projects compared CXR with or without sputum cytology.[5 6] Likely due to the trial designs and the short period of follow-up, no statistically significant differences in lung cancer-specific mortality were detected. However, an increase in early detection and a threefold increase in long-term survival were reported in both arms of the Memorial and Hopkins studies, when compared with the National Cancer Institutes' Surveillance Epidemiology and End Results for unscreened cancers data.[8] At the time, this was attributed to *lead time bias* (ie, the apparent increase in survival observed due to 'preponing' the diagnosis rather than the prolonging of life). Of particular note however, was an unequivocal difference in 5-year survival of early-stage detected cancers between those who had surgical resection (70%) and those who did not (10%) due to either refusal or medical contraindication,[9] suggesting a successful early diagnosis strategy should save lives.

Despite the overall negativity following these early trials, more robust studies were carried out including the Prostate, Lung, Colorectal and Ovarian (PLCO) study which started in 1993. 155 000 smokers and non-smokers aged 55–74 were randomised to have either annual CXR for 4 years or no screening. Disappointingly, the authors reported no effect on lung cancer diagnosis, stage, histology or mortality after 13 years of follow-up.[10] A subanalysis of the efficacy of yearly CXR screening in those at high risk also demonstrated no effect on lung cancer incidence or mortality.

Computed tomography

The Mayo Lung Project, a North American single-arm, LDCT screening pilot carried out in 1999, detected pulmonary nodules in 74% and lung cancer in 4% of those screened. The authors concluded that LDCT could detect early-stage lung cancers but had no significant effect on mortality when compared with subjects screened by CXR in the earlier Mayo Clinic Study. They suggested that LDCT screening had led to overdiagnosis of

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indolent early-stage cancers and that due to the high false positive rate, the risk of complications and expense incurred in the work-up of false positive lesions, the evidence to support LDCT screening was inconclusive.[11 12]

Therefore, the concept of LDCT screening for lung cancer was largely rejected until the Early Lung Cancer Action Project.[13 14] This study increased the threshold for nodule positivity to a diameter of 5mm and consequently only 13% of participants had baseline scans positive for pulmonary nodules. The prevalence lung cancer detection rate was 1.2% of all those screened and 9.7% of positive baseline scans. The majority (85%) of detected lung cancers were stage I, and these patients had an estimated 10-year survival rate of 88%. Only 8% of biopsies revealed benign lesions. These findings dramatically transformed prospects for lung cancer screening and it became apparent that deriving benefit may be possible, but further evidence from well-powered randomised studies was required. Furthermore, this study emphasised the importance of optimising protocols to manage positive screens.

This leads us to the pivotal North American, National Lung Screening Trial (NLST). This was the first well-powered randomised study that compared LDCT screening with CXR in smokers and former smokers aged 55–74. A 20% and 6.7% relative reduction in lung cancer-specific and all-cause mortality, respectively, was observed across the two groups; with a number needed to screen of 320 to save one life from lung cancer after three annual screens and seven years of follow-up.[15] The use of CXR as a control has provoked controversy, as some argue the lack of mortality benefit observed by screening smokers and former smokers in the PLCO trial justifies CXR as equivalent to null screening, while others have argued otherwise.[16] Another limitation of this study is that the majority of NLST participants were younger, white, well-educated and affluent, while higher risk individuals were under-represented. This brings us to two important observations. First, the failure to engage those most at risk of lung cancer in screening in the NLST study may have led to an underestimation of the potential benefit of screening. But second, this study importantly highlights the difficulties faced in undertaking a cost-effective screening approach across society.

NLST radically changed prospects for LDCT screening, but can these data be extrapolated to the UK and Europe? One of the aims of the UK Lung Cancer Screening Trial (UKLS) was to address this and to evaluate costs within the UK National Health Service (NHS).[17] Several other trials in Europe have also recruited, but those that reported on mortality were substantially underpowered and failed to detect a benefit.[18–23] Combining the populations within these studies together with the Dutch-Belgian lung cancer screening trial (NELSON), the Danish Lung Cancer Screening Trial and UKLS will amount to a total of approximately 36 000 participants; although, with varying nodule management algorithms and criteria for eligibility. The pooled results are eagerly awaited by physicians and health providers alike, and should mature in 2016.[24]

LDCT: MANAGEMENT OF PULMONARY NODULES

The studies discussed have clarified the CT features of nodules and growth rates that support benign or malignant diagnoses.[25–30] Several predictive models taking into account clinical and demographic factors, as well as CT and positron emission tomography (PET) features of nodules have been proposed and validated, enabling quantification of risk of malignancy for a given nodule.[31–33] As a result, we can adopt a more conservative approach to certain nodules by employing CT surveillance, reserving the more invasive procedures for higher risk nodules.

In 2005, in response to the growing problem of small CT-detected nodules, the Fleischner Society published a management algorithm.[34] The strategy adopted was a conservative one that mandated that all small nodules should be followed-up in high-risk people (essentially smokers or former smokers). More recent guidelines, published by the American College of Chest Physicians (ACCP),[35] generally mirror the Fleischner guidelines with little change to follow-up recommendations (table 1). The Fleischner Society have recently responded to the problem of the subsolid nodule by publishing a further statement on their management.[36] For those who are at high risk as per the US Preventative Services Task Force (USPSTF) criteria, the Lung CT Screening Reporting and Data System (Lung-RADS) has been specifically created.[37] However, there is emerging evidence that implementation of the ACCP guidelines in the US has been suboptimal and that performance of Lung-RADS may not be as accurate as an approach using the Brock University nodule risk prediction model.[38] Tables 1–3 show the comparison between these various nodule management strategies, which vary considerably.

The British Thoracic Society (BTS) published new guidelines on the investigation and management of pulmonary nodules in July 2015 following a comprehensive review of the evidence, with a third of the references cited from 2012 or later.[39] Importantly, recommendations differ substantially from the earlier guidelines, especially for very small nodules, and recommend higher nodule follow-up thresholds, the use of risk prediction calculators and automated volumetric assessment to clarify follow-up requirements and growth rates (table 4). The inclusion of volumetric measurement will be challenging to implement across the UK but this will be offset by a substantial reduction in follow-up scans compared with previous guidelines. The Brock University risk prediction tool, which was developed from the Pan-Canadian screening cohort[32] and the Herder model, where PET-CT results are available, are recommended to more accurately define risk of malignancy. The role of further imaging, minimally invasive investigations and therapy is reviewed and recommendations made. This guideline also includes a service delivery model.

CURRENT CT SCREENING ACTIVITY INSIDE AND OUTSIDE THE UK

Lung cancer screening by CXR was advocated by the American Cancer Society in the 1970s, however this recommendation was withdrawn following evidence from the trials in the 1980s. Following the publication of the NLST results, the USPSTF recommended screening with LDCT of individuals aged 55–80 who have accrued at least a 30 pack-year smoking history and are current or former smokers who have given up for ≤15 years. The ACCP/American Thoracic Society, American College of Radiology (ACR) and National Comprehensive Cancer Network have all also released statements or guidelines for screening.[40–42]

In February 2015, the US insurers, the Center for Medicare and Medicaid Services agreed to fund screening of asymptomatic insured individuals aged 55–77 who meet the USPSTF smoking criteria.[43] The newly instated ‘Obamacare’ enables some 30% of the uninsured population to access LDCT screening; however, once a nodule is detected it is classified as surveillance rather than screening, and perversely funds are insufficient to cover this crucial aspect of the screening process. Furthermore, a significant proportion of the US population do not qualify for screening at all through lack of insurance coverage. What is really required, therefore, is a national screening programme that is accessible to individuals from all communities such as the US National Breast

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Table 1 Comparison of Fleischner, Lung-RADS and ACCP guideline management of SN detected within or outside of screening

	Fleischner		ACCP		Lung-RADS
	Low risk	**High risk**	**Low risk**	**High risk**	
Baseline scan					
No nodules or nodules with benign features	No follow-up	No follow-up	Not specified		Category 1 (negative): return to annual screening at 12 months
<4 mm		Interval CT at 12 months	Optional follow-up	Interval CT at 12 months then discharge if stable	Category 2 (benign): return to annual screening at 12 months
4–6 mm	Interval CT at 12 months	Interval CT at 6–12 and 18–24 months	Interval CT at 12 months then discharge if stable	Interval CT at 6–12 and 18–24 months and discharge at 24 months if stable	
6–8 mm	Interval CT at 6–12 and 18–24 months	3–6, 9–12 and 24 months	Interval CT at 6–12 and 18–24 months and discharge at 24 months if stable	Interval CT at 3–6, 9–12 and 24 months and discharge at 24 months if stable	Category 3 (probably benign): interval CT at 6 months
8–15 mm	Interval CT at 3, 9, 24 months, dynamic CT chest, PET-CT±histology		Risk<5%: perform CT surveillance at 3–6, 9–12 and 18–24 months If non-FDG avid/ non-enhancing on contrast CT and risk <40% or negative biopsy: perform CT surveillance at 3–6, 9–12 and 18–24 months Risk 5%–65%: perform PET and consider biopsy/resection Risk >65%: PET not required favour histological confirmation, with surgical resection		Category 4A (suspicious): PET-CT: interval CT at 3 months
>15 mm					Category 4B (suspicious): perform standard CT with or without contrast; PET-CT; histology
Interval scan					
<4 mm (new)	Discharge if resolved or at 12 months if no growth		If there is clear evidence of growth (VDT<400 days is suggestive of malignancy), favour surgical resection If no growth or decrease in size, follow-up for 2 years or until nodule disappears		Category 2 (benign): return to annual screening at 12 months
4–6 mm (new)	Discharge if resolved or at 1 year if no growth	Discharge if resolved or at 18–24 months if no growth			Category 3 (probably benign): interval CT at 6 months
<8 mm (new/growing)	Discharge if resolved or at 24 months if no growth	Discharge if resolved or at 24 months if no growth			Category 4A (suspicious): interval CT at 3 months
>8 mm (new/growing)	Perform PET-CT±histology Discharge if resolved or at 24 months if no growth				Category 4B (suspicious): perform standard CT with or without contrast; PET-CT; histology

N.B. Lung-RADS is for CT screening scans only.
ACCP, American College of Chest Physicians; PET, positron emission tomography; RADS, Reporting and Data System; SN, solid nodules.

and Cervical Cancer Early Detection Program.[44] Nonetheless, LDCT screening for insured individuals is now underway in the US. The ACR runs an accreditation programme outlining basic standards for performing and evaluating screening scans using the above-mentioned Lung-RADS.[42] At the time of writing, there were 1220 accredited centres for LDCT screening in the US, 43 of which had been awarded 'diagnostic imaging centre of excellence'. The ACR has constructed a lung cancer screening registry, to record outcomes from screening and the first feedback was expected in autumn 2015.[45]

Screening has not yet been initiated in Canada, and the European Society of Radiology and European Respiratory Society recommend that screening should be performed in 'comprehensive, quality-controlled longitudinal programmes'.[46] In China, several lung cancer screening programmes have been initiated, particularly in areas with high lung cancer incidence, funded by central or local government.[47]

The UK National Screening Committee (NSC) is due to make a decision on lung cancer LDCT screening in the UK pending the results of the pooled European data.[48] In the meantime, several centres around the UK have initiated early diagnosis campaigns or pilot screening projects and these will contribute increasing knowledge around the best methods of implementation in the UK.[49]

PRESENT BARRIERS TO SUCCESSFUL IMPLEMENTATION OF LDCT SCREENING

With these advances in CT technology and pulmonary nodule management, are we now in a position to recommend screening? In 1968, Wilson and Jungner compiled a report commissioned by the WHO highlighting that while the concept of screening was admirable, it was not without difficulties in terms of optimising benefits and harms.[50] In order to aid the appropriate selection of conditions for which the benefits of screening outweighed the harms, they outlined 10 screening principles for appraising the viability, effectiveness and appropriateness of a screening programme,[51] which form the basis for the criteria outlined by the UK NSC. Table 5 lists these 10 principles, and

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Table 2 Comparison of Fleischner, Lung-RADS and ACCP guideline management of PSN detected at baseline screening or incidental scans

	Fleischner	ACCP	Lung-RADS
Baseline scan			
No nodules or nodules with benign features	Interval CT at 3 months	If <8 mm: interval CT at 3 and 12 months and then annually for 3–5 years If multiple, consider each nodule separately	Category 1 (negative): interval CT at 12 months
<6 mm			Category 2 (benign): interval CT at 12 months
≥6 mm with solid component <6 mm			Category 3 (probably benign): interval CT at 6 months
≥6 mm with solid component 6–8 mm			Category 4A (suspicious): interval CT at 3 months; PET-CT if solid component >8 mm
≥6 mm with solid component ≥8 mm		Interval CT at 3 months+PET if solid component >8 mm N.B. If >15 mm, consider PET+biopsy/resection at baseline	Category 4B (suspicious): standard CT with or without contrast; PET-CT if solid component ≥8 mm; histology
Interval scan			
<6 mm nodule	Persistent nodules with solid component <5 mm: perform annual CT for minimum 3 years	Annual CT for 3–5 years. Any growth or development of solid component should prompt further investigation/resection	<6 mm nodule: category 2 (benign): interval CT at 12 months
≥6 mm with smaller solid component			≥6 mm nodule solid component <6 mm (or new nodule <6 mm on interval CT): category 3 (probably benign): interval CT at 6 months
≥6 mm with larger solid component	For persistent solitary nodule or multiple nodules with one dominant nodule with solid component >5 mm: favour biopsy/resection (PET-CT if nodule >10 mm)	Perform PET-CT+biopsy/resection	≥6 mm nodule with solid component 6–8 mm (or new or growing solid component <4 mm): category 4A (suspicious): interval CT at 3 months
			≥6 mm with solid component >8 mm or new or growing solid component >4 mm: category 4B (suspicious): standard CT with or without contrast; PET-CT; histology depending on Brock risk

N.B. Lung-RADS is for CT screening scans only.
ACCP, American College of Chest Physicians; PET, positron emission tomography; PSN, part-solid nodules; RADS, Reporting and Data System.

Table 3 Comparison of Fleischner, Lung-RADS and ACCP guideline management of pGGN detected at baseline screening or incidental scans

	Fleischner	ACCP	Lung-RADS
Baseline scan			
<5 mm	No follow-up if solitary, but if multiple, perform interval CT at 2 and 4 years	No follow-up	See below
>5 mm	Interval CT at 3 months, then annual for minimum 3 years (for solitary and multiple nodules)	Annual CT surveillance for minimum 3 years (follow-up at 3 months if >10 mm)	
<20 mm	As above		Category 2 (benign): interval CT at 12 months
≥20 mm			Category 3 (probably benign): interval CT at 6 months
Interval scan			
New nodule <20 mm	As for baseline scan	If >10 mm and persistent or growing favour resection	Category 2 (benign): interval CT at 12 months
≥20 mm and stable or slow growth			Category 3 (probably benign): interval CT at 6 months
Persistent nodule	Annual CT surveillance for a minimum of 3 years Favour excision if nodule >10 mm or multiple pGGN with a persistent dominant nodule Biopsy noted to have low yield		>20 mm and stable or slowly growing=category 2 (benign): interval CT at 12 months

N.B. Lung-RADS is for CT screening scans only.
ACCP, American College of Chest Physicians; pGGN, pure ground glass nodules; RADS, Reporting and Data System.

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Table 4 Summary of BTS guidelines for management of pulmonary nodules detected at baseline screening or incidental scans

	Solid nodules	Part solid nodules	Pure ground glass nodules
Baseline scan			
<5 mm or <80 mm^3	Discharge	Discharge	
5–6 mm	CT at 12 months	Interval CT at 3 months	
≥6 to <8 mm or 80 to <300 mm^3	Interval CT at 3 and 12 months		
>8 mm or >300 mm^3	1. PET-CT 2. Assess Herder risk ▶ If <10%: do CT at 3 and 12 months ▶ If >10%: consider biopsy or resection or CT surveillance on individual basis ▶ If >70% favour resection		
Interval scan			
2D		If stable or smaller, assess Brock risk at 3 months ▶ If risk <10%, continue CT surveillance at 1, 2 and 4 years (or until nodule disappears) ▶ If risk >10% or concerning morphology, consider histological diagnosis and discuss options with patient ▶ If growth or altered morphology (especially if growth of solid component by ≥2 mm) favour further work up and definitive management N.B. Consider PET if solid component ≥8 mm	
Stable nodule	Discharge after 2 years		
Growing	PET-CT and Herder score		
3D			
Stable or slow growth	Discharge if stable, and discharge or ongoing surveillance if slow growth (VDT>600 days)		
VDT 400–600 days	Further surveillance or biopsy or resection are acceptable, and decision should be based on patient preference		
VDT ≤400 days	Further work up, and consider definitive management		

BTS, British Thoracic Society; PET, positron emission tomography; 2D, two-dimensional; 3D, three-dimensional.

proposes key factors that need to be addressed for successful implementation of a lung cancer screening programme. These factors are discussed below.

Radiation risk

Advances in CT scanning technology have improved nodule detection and characterisation while reducing radiation dose. Techniques such as iterative reconstruction (which reduces the extent of noise and artefact associated with images at lower radiation doses), altering tube voltage, current and gantry rotation speed are valuable in reducing effective radiation doses. Further reduction to overall radiation exposure over time will follow implementation of the more conservative approaches to managing positive findings, suggested in the more recent guidelines.[52] Nevertheless, radiation risk will remain a problem and always needs to be considered when balancing risks and benefits.

Overdiagnosis and false positives

Overdiagnosis is the detection and characterisation of disease that would not otherwise cause harm. It may be minimised in LDCT screening by taking into account morphological features that denote more indolent cancers that may be managed with a more conservative approach less likely to cause harm. False positives are benign lesions that undergo investigation and may therefore result in harm, both physical and psychological. Pure ground glass nodules[53] and solid and subsolid nodules with longer volume doubling times are more likely to be indolent[30] or benign. The recent BTS guidelines support a more conservative management of volumetrically assessed, potentially indolent or benign lesions, thus reducing the rate of overdiagnosis and benign histological diagnoses.

Optimal eligibility criteria for screening

It is clear that overdiagnosis rates, false positive rates, the number needed to be screened to save one life from lung cancer and cost of screening can all be reduced by selecting the higher risk population.[54] However, what the appropriate threshold for risk is, and how this interacts with entry and exit age, competing mortality and fitness are complex. Randomised trials of LDCT screening have adopted a number of different approaches in determining who to invite to screening. The UKLS sent out questionnaires which enabled determination of the Liverpool Lung Project lung cancer risk prediction algorithm and had a relatively high lung cancer detection rate (2.1%),[55] while the NLST used just age and smoking status. Which risk assessment tool most appropriately balances simplicity and predictive accuracy still needs to be determined. Furthermore, based on the results from the NELSON study, screening interval may also need to be varied by risk. They showed that interval cancers occur at a low rate (1%) and this occurrence was associated with age but not smoking status.[56] Further research into other factors predictive of interval cancers is needed. With ongoing research into potential biomarkers, LDCT screening may one day be offered to a wider demographic and include non-smokers with a positive biomarker test.

Balance of psychological impact

The psychological burden of screening remains to be determined, and for the individual, may in large part depend on the severity

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Table 5 Current issues to be addressed for implementation to lung cancer LDCT screening in the UK with reference to Wilson and Jungner[50] criteria

WHO Wilson and Jungner[50] criteria	Met	Key factors for implementation
1. The condition sought should be an important health problem	Yes	
2. There should be an accepted treatment for patients with recognised disease	Yes	
3. Facilities for diagnosis and treatment should be available		Resource implications and availability of volumetric assessment
4. There should be a recognisable latent or early symptomatic stage	Yes	Overdiagnosis and false positive rates
5. There should be a suitable test or examination	Yes	Radiation risk
6. The test should be acceptable to the population	Yes	Balance of psychological impact
		Equitable access, uptake and adherence to screening across the population
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood	Yes	
8. There should be an agreed policy on whom to treat as patients		Optimal eligibility criteria for screening
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	Yes	Co-implementation of smoking cessation Incidental findings from screening
10. Case-finding should be a continuing process and not a 'once and for all' project		Interval cancer rate
		Regulating CT screening

LDCT, low dose CT.

of the screening result and psychosocial characteristics. To date, most studies of trial participants undergoing lung screening have shown that the anxiety and distress associated with false positive screens are minimal and short-lived.[57] Clinically, meaningful changes in health-related quality of life were observed one month after the detection of an indeterminate pulmonary nodule, but returned to prescreening levels after two years, suggesting no long-lasting effects.[58 59] However, this is yet to be studied in the community context and there is evidence from other screening programmes for long-term psychological distress.[60] Furthermore, given a significant proportion of screening participants will at one time receive a false positive or indeterminate result, further research is needed to monitor the psychological impact of the surveillance process, examine individual differences in response and develop strategies which minimise harm. Qualitative evidence suggests effective communication about indeterminate nodules by health professionals could be one such strategy,[61] and ensuring patients are well-informed about the screening process and possible results will be essential. In addition, there is concern that an 'all clear result' could be falsely interpreted to mean low future risk of developing lung cancer, and a lower susceptibility to the effects of smoking. This issue of over-reassurance has been studied for other cancer types, with evidence that it may compromise future symptom appraisal and delay symptomatic help-seeking.[62] Care must therefore be taken to tailor individual communication, so as to minimise adverse psychological responses to screening and any negative impact on future health behaviours.

Incidental findings from screening

Incidental findings are often viewed as a negative aspect of CT screening, but their detection may also provide an opportunity to rectify other conditions that threaten quality of life or survival. The NLST reported a 6.7% reduction in all-cause mortality, an effect most pronounced in Black African–Americans.[15 63] This may be explained by detection of clinical and radiological findings in the process of screening, and due to the improved access to healthcare brought about by screening that may prompt intervention for non-lung cancer co-morbidities.[64] Several studies have shown that ungated LDCT scans can accurately predict coronary calcium and subsequent cardiovascular events comparable to formal coronary calcium scoring.[65 66] Those at high risk of lung cancer are also at higher risk of cardiovascular disease, and combining risk assessment and screening provides opportunity to improve outcomes for both conditions. However, further prospective studies are needed. LDCT scans have also been shown to be useful for detecting emphysema,[67] which is a recognised risk factor for lung cancer, and osteoporosis which was associated with all-cause mortality in the NELSON cohort.[68]

Co-implementation of smoking cessation

Achieving smoking abstinence in combination with LDCT screening has been reported to almost double the reduction in lung cancer mortality compared with screening alone within the NLST participants,[63] but the impact of screening on smoking cessation is unclear. Several studies have reported increased smoking cessation in trial participants compared with the background population. However, no significant differences in outcomes between the screened and control groups have been noted, suggesting that trial participants may be a more motivated group.[69–75] Few studies have noted an increase in the number of participants abstaining from smoking with successive positive or indeterminate screen results compared with those with negative screens.[76–78] The optimal method of promoting smoking cessation in screening participants has not been determined. Further studies of patients, rather than trial participants, in the real-life screening context are needed to further explore this.

Resource implications and availability of volumetric assessment

Several studies, based primarily on US data, have reported varying Incremental Cost Effectiveness Ratios per quality of life

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adjusted life year (QALY) gained, ranging from US$28 000 to over US$100 000.[79–81] The cost of lung cancer screening in the UK is not known, but has been estimated to be around £9000 per QALY gained;[55] well below the threshold of £30 000 deemed acceptable by the National Institute for Health and Care Excellence. If NLST eligibility criteria were to be implemented, an estimated 8.7 million people in the US may be eligible for screening.[82] The size of the UK lung cancer screening eligible population is unclear, however, even assuming uptake levels may be low (in the region of 50%), numbers are likely to be significant. This has considerable resource implications in terms of carrying out the baseline and interval CT scans required for nodule follow-up.

Most hospitals now have the technology to perform LDCT scans and take advantage of many of the other CT advances such as Maximum Intensity Projections (which allow enhanced visualisation of high attenuating structures such as nodules) and Multi-Planar Reconstruction (where images are reconstructed in customised planes). Automated estimation of the volume of nodules, calculated by mapping the CT attenuation values, is also possible with modern volumetric nodule assessment packages. These packages also autocalculate volume doubling times, which can more accurately quantify growth of a nodule than conventional two-dimensional measurements.[83] However, exactly what proportion of UK hospitals currently has access to the technical, radiological and clinical know-how to implement volumetric assessment needs to be determined.

Various strategies as outlined above including appropriate selection criteria for screening and improved management of pulmonary nodules will help reduce the cost of screening. The cost of various methodologies that can be used in the screening process, such as the use of mobile CT scanners versus dedicated screening centres, also needs to be evaluated. Scan reading time is also a factor, and research is needed to explore whether there are feasible options that will relieve some of the work from radiologists.

Equitable access, uptake and adherence to screening across the population

Participation in national screening programmes for breast and colorectal cancer is around 70% and 60%, respectively,[84–87] but there is evidence to suggest this will be lower in future lung cancer screening programmes. In the NELSON trial, 32% of the approached persons (aged 50–75 years) in the general population responded to an initial questionnaire on general health, lifestyle and smoking history (which did not mention the NELSON trial[88]), similar to the response rate for the UKLS pilot randomised control trial.[89] In NELSON, 19% (6% overall) of these were at high risk and half gave informed consent and were recruited. In UKLS, only 11.5% met the risk threshold for trial entry (higher than for NELSON) and a similar proportion were recruited. Although participation in a trial might be less than in a screening programme, in both of these well-conducted studies the participation rate of higher risk people was low enough to be of concern for implementation.

UKLS also showed that current smoking and low socioeconomic status (SES) were associated with lower uptake, a problem observed across European and US trials[90 91] and for other cancer screening programmes more widely.[92] Lung cancer prevalence is higher in lower SES communities, where lifelong smokers are both over-represented[93] and more tobacco-dependent.[94] Indeed, over 40% of the lung cancers detected in UKLS were in people from the most deprived quintile. Reported barriers to participation among smokers include concern about risk of lung cancer, a lower perceived benefit of early detection, perceived blame and stigma and fearful, fatalistic and nihilistic beliefs around lung cancer outcomes.[95–97] In addition, methods of recruitment, which demand significant correspondence from potential participants (as required by most trials), are likely to increase attrition among lower SES groups. A UK study has begun recruitment to a trial examining a tailored invitation method designed to overcome these barriers and reduce inequalities in participation (Quaife *et al*, manuscript in preparation).

Factors affecting screening adherence may be similar to those affecting uptake, with the added complexity of psychological responses to positive and negative results received in previous screening rounds.[98] Given that the ratio of screening benefit to risk increases with lung cancer risk, promoting engagement of the higher risk and hard-to-reach groups aims to reduce lung cancer inequalities and improve the cost-effectiveness and efficacy of screening.

Regulating CT screening

Any screening programme needs to have stringent audit and quality control to ensure compliance with best practice. Availability of adequate resources to successfully implement and deliver such a programme to a high standard is vital. Controls also need to be in place to ensure uniformly low radiation doses are used, scans are read to an adequate level of accuracy and that nodules and other findings are appropriately managed. A database to record outcomes is crucial to enable measurement of screening outcomes and further develop and improve the protocols used for all aspects of screening.

CONCLUSION

LDCT screening is undoubtedly a promising method to improve lung cancer outcomes. If lung cancer screening is to be initiated in the UK, adequate provision of resources is essential, with employment of stringent screening protocols and regulatory processes to ensure benefits outweigh harms and costs are minimised. Although it is acknowledged that the UK NHS is under considerable resource pressure, lung cancer is a condition that has not seen the improved outcomes observed in other cancers. With an overall 5-year survival for lung cancer in the UK <13%[2] and the limited efficacy of available treatments for late-stage disease, there seems to be no alternative but to proceed with screening to improve rates of early detection and curative treatment.

Author note We are sad to announce that Professor Jane Wardle passed away whilst this paper was in preparation. Jane had a phenomenal wealth of experience, knowledge and understanding of cancer screening and as an academic she was an inspiration to all who knew her. She is deeply missed by all of her co-authors and colleagues.

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