Review Article

Lung cancer screening in 2022: a narrative review

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Background and Objective: In recent years, strong evidence has emerged supporting the implementation of lung cancer screening. The impact of the widespread introduction of screening on lung cancer services, including the anticipated increase in thoracic surgical activity, must be considered. This review explores the evidence underpinning lung cancer screening, identifies challenges, and outlines potential strategies to facilitate the successful implementation of such programs.

Methods: A literature search on aspects of lung cancer screening was performed using PubMed from inception to May 2022. Topics included low dose CT lung cancer screening, harms of screening, targeted screening methods, service delivery, and surgical management of early stage lung cancer. Emphasis was placed on randomised controlled trials (RCTs) and clinical guidelines.

Key Content and Findings: Targeted screening offers a 20–24% lung cancer mortality reduction by diagnosing disease at earlier stages, when the gold standard treatment of surgical resection is possible. Screening brings risks of harm, such as overdiagnosis of indolent disease and healthcare resource use. Pilot screening programmes offer lessons to mitigate these harms in practice, and healthcare systems are increasingly interested in implementing national screening programmes as technological advances improve safety and cost-effectiveness. Prospective research into participant selection, nodule management, and treatment strategies are ongoing.

Conclusions: An increasing caseload of curable lung cancer compels leverage of surgical and non-surgical treatments for lung cancer and related comorbidity to further enhance the effectiveness of screening.

Keywords: Lung cancer; early detection; screening; thoracic surgery; Lung Health Checks (LHC)

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Introduction

Lung cancer is the most common cause of cancer death globally, estimated to have caused 18% (9.9 million) of cancer deaths in 2020 (1). It is also the most common cause of cancer death in the United Kingdom (UK), representing more than one-fifth (n=35,100) of all patients dying from cancer in 2018 (2). Half of these deaths occur under 75 years of age. The 5-year survival rate is 15%, putting it among the five cancer types with the poorest outcomes (3). A major reason for this is its insidious onset, leading to delayed symptoms and clinical presentation once disease has advanced. Indeed, 71% of lung cancers are diagnosed at stages III–IV. One-year survival with

stage IV (metastatic) disease is 17%, compared to 83% with stage I (4). A key determinant of survival is stage at diagnosis, as resection of early-stage disease conveys the greatest survival advantage (5).

Encouragingly, the proportion of patients with lung cancer undergoing surgery in the UK, although low, is increasing. This correlates with the data reported by the Society for Cardiothoracic Surgery in Great Britain and Ireland who have tracked lung cancer surgery since the 1980s (6). The third national thoracic surgery activity and outcomes report from 2018 contains data on patients undergoing lung cancer surgery from 1980 to 2015 and highlights that prior to 2006, overall lung cancer surgery activity in the UK remained relatively static at approximately 4,000 cases per year. However, numbers have risen steadily over the last decade, with over 7,000 procedures performed across the UK in 2015 (6). Despite this increase in the number of resections for lung cancer, the UK was recently ranked 21st out of 27 European countries based on lung cancer five-year survival rates (6).

Resection rates

The UK has historically had a particularly low resection rate for non-small cell lung cancer (NSCLC), with fewer than 20% of patients undergoing surgery with curative intent. The National Cancer Registration and Analysis Service reported that the approximate proportion of patients with NSCLC undergoing surgery was only 16% between 2013 and 2015. Nevertheless, this represents a marked increase from the 8.8% and 11% quoted for 1998 and 2008 respectively (7). However, contemporaneous studies from European countries such as Finland and Iceland report resection rates in excess of 25% (8,9).

Whilst this overall increase in the number of lung resections being performed is encouraging, the degree of variability between different regions of the country remains a concern and highlights the important role played by the infrastructure of regional cancer networks in facilitating radical treatment for patients with lung cancer. The resection rate is calculated by considering the number of people who underwent surgical resection for lung cancer against the number of people diagnosed with lung cancer in a given time period. Nationally collected data from 2017 reported regional resection rates ranging from 13–30% (10). Perhaps more salient is a further analysis of resection rates, undertaken as part of the same body of work and focussing solely on those patients most likely to be suitable to undergo radical surgical resection. Limited to patients with a performance status score of 0–2 and early stage (stage I/II) lung cancer, regional resection rates again varied from 51–93%. It has been calculated that if all thoracic surgical centres were able to increase their resection rates for these early-stage patients to 78% and over (as currently seen in the six centres in the country with the highest resection rates), more than 1,000 additional lung resections would be performed every year, which itself could further improve overall survival for patients with lung cancer throughout the whole of the UK (10).

Broadly, the two factors underpinning the selection process for lung resection are operability, where patients must be fit enough to undergo surgery, and resectability, where patients must have a pattern of disease for which the operating surgeon is confident of achieving a complete resection. Unfortunately, only a minority of patients have resectable disease. Moreover, an important proportion of patients with lung cancer are frail and comorbid, rendering them prohibitively high risk to undergo the rigours associated with major thoracic surgery. Whilst the high incidence of lung cancer in comparison to other malignancies undoubtedly plays a key role in making lung cancer the leading cause of death worldwide (11), the combination of a high incidence of metastatic disease and a low rate of radical treatment also accounts for its poor prognosis. Furthermore, lung cancer surgery has historically been performed by surgeons engaging in a mixed cardiothoracic practice. The role of the dedicated thoracic-only cardiothoracic surgeon is a relatively novel concept.

It is well recognised that the two of the most important approaches to improving overall lung cancer survival are increasing the proportion of patients undergoing surgery and reducing the rate of post-operative morbidity and mortality in this same patient cohort. In stark contrast to 1-year survival figures for lung cancer patients as a whole (which are around 40%) (7). One-year survival for lung cancer patients who have undergone surgery with curative intent is approximately 88% (10). This is because most patients undergoing surgery have early-stage disease. Hence, if more patients with early-stage lung cancer can be identified, offered and successfully treated with radical surgical resection without complications, it is likely to have a significant impact on overall lung cancer survival rates; if these patients survive the peri-operative period they are much more likely to survive to 5 years and beyond in comparison to patients with lung cancer who do not

undergo surgery (12).

Objectives

Increasing availability of lung cancer screening is likely to have major impacts in thoracic oncology and allied disciplines. A wealth of evidence has accumulated in the past decade, with marked advancement in our understanding of lung cancer risk, diagnosis, and management. This review aims to outline the strengths and weaknesses of lung cancer screening as it relates to the thoracic surgical community, which is intrinsic to translating the diagnostic advances brought by screening into improved patient outcomes. We present the following article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-22-10/rc).

Methods

Literature relating to lung cancer screening and the surgical management of early stage lung cancer was searched by the authors via PubMed up to May 2022. Reference lists were reviewed to identify further relevant sources. Topics included low dose CT lung cancer screening, harms of screening, targeted screening methods, service delivery, and surgical management of early stage lung cancer. Emphasis was placed on randomised controlled trials (RCTs) and clinical guidelines, particularly those relating to UK practice.

Lung cancer screening

Through the 1990s, low dose computed tomography (LDCT) emerged as an effective test for lung cancer (13-15). The first large-scale RCT performed to investigate the effect of LDCT as part of lung cancer screening was the National Lung Screening Trial (NLST) (16). This US-based study enrolled 53,454 individuals at elevated risk of lung cancer between 2002 and 2004, assigning half to the intervention arm for three annual LDCT scans and half to annual chest radiography. Lung cancer was detected through screening in 2.4% of the LDCT arm and in 1.0% of the chest X-ray (CXR) arm. Overall, 70% of LDCT-detected cancers were stage I–II, compared to 57% in the CXR arm. A total of 61% (n=642/1,060) of lung cancer cases in the LDCT group received surgical treatment. For the primary outcome of lung cancer-specific mortality, the LDCT arm had a 20% relative risk (RR) reduction (95% CI: 6.8–28%, P=0.004). For every 320 participants screened using LDCT, one lung cancer death was averted. There was also a 6.7% relative reduction of overall mortality (95% CI: 1.2–14%, P=0.02).

The other, more recent, large RCT was the Dutch-Belgian NEderlands-Leuvens Longkanker Screenings ONderzoek (NELSON) trial, which compared LDCT to usual care in a European setting (17). Here, 15,789 participants were allocated to either four rounds of LDCT screening over 5.5 years or no screening. Outcomes were monitored over a minimum of 10 years, up to the end of 2015. The primary outcome of lung cancer-specific mortality in men (who represented more than 85% of total study participants) found an RR reduction of 24% (RR 0.76, 95% CI: 0.61–0.94, P=0.01) in favour of screening.

In total, nine RCTs have investigated LDCT screening, as summarised in *Table 1* (16-24). Smaller trials have provided mixed results. A meta-analysis was recently performed to examine the pooled effects of screening from all published RCTs, which together randomised 94,921 participants (24). This found LDCT screening to be associated with a 16% relative reduction in lung cancer mortality (RR 0.84, 0.76–0.92) and a 3% reduction in all-cause mortality (RR 0.97, 0.94–1.00). When compared to existing forms of mass screening, lung cancer screening is estimated to bring a maximum difference in all-cause mortality of 10 deaths per 1,000 participants at 15 years, compared to four deaths prevented by breast cancer screening by 25 years, and two deaths due to colorectal cancer screening after 10–20 years (25). The substantial improvement in lung cancer mortality demonstrated in randomised trials provides compelling evidence of the benefit of lung cancer screening.

Lung cancer screening has been widely offered in the USA since 2013, when the US Preventive Services Task Force (USPSTF) published its recommendation following the publication of the NLST, with the Canadian Task Force on Preventive Health Care following suit in 2016 (26,27). Many other countries are considering the feasibility of implementation in the context of their health services and populations (28-31). In the UK, NHS England has undertaken a pilot Targeted Lung Health Check (TLHC) programme in more than 20 areas with high lung cancer incidence, with the anticipation of reaching 600,000 eligible participants (32,33). This is built on a number of smaller locally arranged pilot programmes, including Manchester and Liverpool, as their promising results aligned well with the NHS Long Term Plan's ambitious goal of increasing

Table 1 Randomised controlled trials of lung cancer screening using low-dose computed tomography

Trial	Control group	Study period	Screening intervals	Follow-up interval (y)	Eligibility: age (y); smoking exposure; quit duration (y)	Sample size	False positive rate (%)	Surgical resection rate (%)	Benign resection rate (%)	LC-mortality effect [RR/HR (95% CI)]
NLST (16), USA	CXR	2011–2019	0-1-2	6.5	55–74; ≥30 py; ≤15	53,454	23.3	61	24	RR 0.85 (0.75–0.96)
NELSON (17), NL/Belgium	Usual care	2006–2020	0-1-3-5.5	10	55–75; 15/d for 25 y or 10/d for 30 y; <10	15,774	3.6	–	–	Males: RR 0.76 (0.61–0.94), P=0.01; females: RR 0.67 (0.38–1.14)
Dépiscan (18), France	CXR	2002–2004	0-1-2	Baseline	50–75; 15/d for 20 y; <15	621	–	–	–	–
DANTE (19), Italy	Usual care	2008–2018	0-1-2-3-4	8.4	60–74; 20 py; <10	2,472	14.5	70	19	RR 1.01 (0.70–1.44)
DLCST (20), Denmark	Usual care	2012–2016	0-1-2-3-4	9.8	50–70; 20 py; <10	4,104	7.9	65	18	RR 1.03 (0.66–1.60)
ITALUNG (21), Italy	Usual care	2004–2014	0-1-2-3	9.3	55–69; 20 py; ≤10	3,206	28.8	81	5.5	RR 0.70 (0.48–1.04)
MILD (22), Italy	Usual care	2005–2018	5 annual or 3 biennial	10	≥49; 20 py; <10	4,099	12.0	84	9.0	HR 0.61 (0.39–0.95), P=0.02
LUSI (23), Germany	Usual care	2007–2018	0-1-2-3-4	8.9	50–69; 15/d for 25 y or 10/d for 30 y; <10	4,039	25.5	–	30	HR 0.74 (0.46–1.19), P=0.21)
UKLS (24), UK	Usual care	2011–2020	0	10	50–75; [†]LLPv2 ≥5%	4,055	3.6	83	10	RR 0.52 (0.35–0.77), P=0.001

[†]LLPv2: Liverpool Lung Project version 2 risk prediction model was used to determine eligibility in UKLS trial instead of categorical smoking criteria. CXR, chest X-ray; NL, Netherlands; d, day; y, years; py, pack-years; LC, lung cancer; RR, relative risk; HR, hazard ratio; CI, confidence interval.

detection of all cancers at early stage from half to three quarters by 2028 (34-37). At the time of writing, the UK National Screening Committee has made a provisional recommendation for targeted lung cancer screening in the UK. Subject to public consultation, this will likely lead to a national screening programme (38).

It was demonstrated that lung cancer screening programmes would yield a significantly higher proportion of early-stage lung cancers suitable for treatment with radical surgery. Indeed, several UK trials, including the UK Lung Cancer Screening (UKLS) trial and a further pilot study in Greater Manchester found that lung cancer was detected in 2–3% of patients, of which, importantly, more than 80% were early stage (stage I/II) lung cancers (35,39). Whilst patients must still be physiologically suitable to undergo surgery, these findings suggest that a much greater proportion of patients with screen-detected lung cancer are likely to undergo surgery, in comparison to the overall population of patients with newly diagnosed lung cancer. This conclusion is supported by the results of the clinical trials, where 61–84% of patients with screen-detected lung cancer underwent surgical resection with curative intent (*Table 1*). Real-world implementation may bring different resection rates to those of formal trials, but so far appear to be comparable. Following a baseline screening round in five UK pilot programmes (n=11,148 screened), the surgical resection rate was 66% (n=165/250 lung cancers) (40). Outcome rates can also change over time. In a 5-year Canadian cohort study, 80% (n=137/175) of cancers were detected at the baseline screening round, with 5–10% of the cancers diagnosed in subsequent rounds (41). The resection rate in NLST at baseline 'prevalence' round was 69% (n=202/292), but this dropped to 42% (n=440/1,059) across the subsequent two annual 'incident' rounds (16,42). In the implementation pilot in Manchester, resection rate changed from 65% (n=30/46 lung cancers) at baseline to 42% (n=9/19) after a 1-year interval (35,36). Widespread adoption of screening is therefore highly likely to lead to further increases in surgical activity, particularly around the time of an initial screening round. Although an exciting prospect, such numbers also represent a challenge in ensuring that existing services are reconfigured in order to cope with such a significant increase in numbers over a relatively short space of time.

Balancing the benefits and harms of screening

As with any medical intervention, screening may cause harm to a proportion of those taking part. Screening harms take a number of forms, not least the direct complications arising from procedures performed to investigate and treat abnormalities identified through imaging. Screening also requires significant healthcare resource utilisation, which needs to deliver value to the population it serves.

False positives and nodule management protocols

As for all clinical tests, the diagnostic performance of LDCT scanning is imperfect. All positive results are relayed to participants, and a proportion of these are anticipated to not represent malignancy, i.e., false positives. There is also significant distress, medicolegal implications, and loss of public trust in screening if cancers are missed (false negatives), resulting in delayed diagnosis with more advanced lung cancer (43).

The NLST considered any non-calcified pulmonary nodule to be a positive result, leading to further investigation at the discretion of treating clinicians. This led to 23% of all scans (n=17,479/75,126) being falsely positive (16). Since then, nodule management protocols have evolved such that most nodules that NLST considered positive would now be considered 'indeterminate', able to be handled with surveillance imaging alone. The American College of Radiologists has developed the Lung Imaging Reporting and Data System (Lung-RADS) protocol, which stratifies the risk of malignancy associated with a nodule and recommends either a screening interval or further investigation accordingly (44). Had the Lung-RADS nodule management protocol been applied in NLST, only 1.8% of individuals would have had a false positive scan (45). Notably, most screen-detected nodules are not malignant. NELSON data showed that nodules ≥10 mm diameter have a lung cancer probability of 15% (46). Further evaluation of suspicious nodules is undertaken prior to committing to surgery. This can include interval imaging for indeterminate lesions to determine volume doubling time (VDT), and/or positron emission tomography (PET) to identify aggressive lesions.

The merits of nodule management protocols in practice are continually being evaluated, particularly as guidelines are updated in light of evolving evidence. The Lung-RADS and PanCan protocols are currently being directly compared in the International Lung Screening Trial (ILST), which will provide insights into their comparative clinical impact (47,48). A summary of findings from the baseline screening rounds of trial and pilot screening programmes in the UK [all but one of which used the British Thoracic

Society (BTS) guideline (49)] reported 4.2% (n=469/11,148) positives and 2.0% (n=219/11,148) false positives, giving a positive predictive value of 47%. Of those without lung cancer, 0.6% (n=61/10,898) had invasive investigations and benign resections were performed in less than 0.1% (n=8/10,898) (40).

Overdiagnosis

Screen-detected lung nodules, by definition, have not caused symptomatic disease at the time of LDCT. In the absence of screening, some would develop into fatal malignancies, but a proportion would remain indolent for the individual's lifetime. By drawing indolent disease into the screen-detected cancer group, a screening programme can look more effective when these individuals go on to survive the follow-up period, a bias known as the 'length time effect'. Conversely, more aggressive cancers are less likely to be detected by screening as they have a shorter preclinical phase. Identifying clinically insignificant lesions through screening, and subjecting participants to invasive tests and treatment, leads to a degree of harm with no benefit. This is referred to as 'overdiagnosis' which may be followed by 'overtreatment'. Overdiagnosis is a notable issue in breast cancer screening, where it is estimated to account for 19% of breast cancers diagnosed, or three overdiagnoses per breast cancer death prevented, and it is why prostate specific antigen screening is not recommended (50-52).

Overdiagnosis is a typical feature of screening, as the aim is to diagnose asymptomatic disease in order to consider intervention. While radiological features (ground glass, spiculation, VDT) and risk prediction tools (e.g. Brock, Herder, PanCan) to predict malignancy risk are helpful, the true pathological potential of a given nodule is often unclear (47,49,53,54). Consequently, long-term data from patients included in lung cancer screening trials are awaited by surgeons with great interest, as such outcomes will undoubtedly shape future surgical practice.

Estimating the degree of overdiagnosis in a trial requires a substantial follow-up period. More cases of lung cancer are detected during initial rounds of screening, but screening does not prevent lung cancer—the same number of cases should be detected eventually in both arms of a large trial. The elevated lung cancer detection in the initial years of a trial reflects the 'lead time effect', whereby disease is detected earlier than it would have been if detected following symptomatic presentation. Of note, introducing a lead time effect is an explicit goal of early diagnosis, not an undesirable systematic error, although it should be taken into consideration when comparing screened groups to control groups.

In order to see beyond lead time and length time effects, enough time must elapse after a screening programme commences to detect a difference in outcomes between the groups. Survival time refers to the interval between diagnosis and death, which is susceptible to the lead time effect, so the preferred outcome in trials is mortality rate from the time of randomisation. In NLST, the initial reported lung cancer incidence was higher in the LDCT group after median 6.5 years since randomisation (RR 1.13, 95% CI: 1.03–1.23) and indeed this gap closed after extended follow-up (after median 11.3 years, RR 1.01, 95% CI: 0.95–1.09) (55). This change corresponded to an estimated overdiagnosis rate of 18.5% decreasing to 3% after longer observation. Similarly, NELSON's epidemiological overdiagnosis rate dropped from 20% at 10 years after randomisation to 8.9% at 11 years (17). There is ongoing uncertainty about the extent of overdiagnosis in lung cancer screening, and its impact on cost-effectiveness, although now that longer follow-up data are available it appears to be less pronounced than initially feared. When reliable nodule risk stratification tools are used, lower false positive rates bring less overdiagnosis and less overtreatment.

Targeted screening

In order to focus screening efforts on individuals at highest risk, eligibility criteria for screening must be applied. There is currently no evidence to support screening in never smokers (56). In the US, eligibility is determined through categorical criteria (USPSTF 2021 criteria: age 50–80 years, smoking history of 20 pack-years or more, and are either a current smoker or have quit within the last 15 years; the previous USPSTF 2013 criteria more closely matched NLST: age 55–74 years, smoking history of 20 pack-years within the past 20 years) (26,57,58). Alternatively, risk prediction models can be used to estimate the risk of lung cancer for an individual within a given time period, and screening eligibility can be based on a threshold percentage risk. In the UK, the TLHC programme uses the Prostate, Lung, Colorectal and Ovarian model 2012 ($PLCO_{m2012}$) and Liverpool Lung Project (LLP) model (59,60). Others with promising validity include the Lung Cancer Risk Assessment Tool (LCRAT), Lung Cancer Death Risk Assessment Tool (LCDRAT), and Bach models, which were shown to have good discrimination [area under the curve

(AUC) range, 0.75 to 0.79] and calibration (observed to expected ratio range, 0.92 to 1.12) through retrospective external validation in large US cohorts (61). An alternative approach to determining eligibility incorporates the risk of cancer against the risks of competing causes of death, in order to select those who have most life-years to gain from screening [Life-Years gained From Screening-CT (LYFS-CT) model] (62). Whilst their relative complexity of risk prediction models has precluded their recommendation by the USPSTF, analyses of large trial and national registry datasets have found them to have the potential to avert more lung cancer deaths, gain life-years, and be more cost-effective, than categorical approaches (63-67). Clinical trials are underway to prospectively test the performance of risk models in UK (Yorkshire Lung Screening Trial) and other European populations (4-In-The-Lung-Run) (29,68).

Radiation

The application of ionizing radiation to large populations for screening purposes warrants consideration as a potential harm, particularly as the target population has already received a prolonged carcinogenic insult from smoking. Radiation doses in screening LDCTs are lower than 'standard' dose diagnostic CTs of the chest (<2 *vs.* ~8 mSv), and, as technology advances, doses have reduced further ('ultra-low dose' <1 mSv). The exact risks of radiation exposures <50 mSv, if any, are a matter of ongoing debate, as estimates are extrapolated from Japanese nuclear bomb survivors and paediatric populations (69-73). It has been estimated that over 10 years of annual screening with 1 mSv LDCTs, the risk of developing cancer is 0.05% (74). This equates to 1 radiation-induced cancer for every 108 screen-detected lung cancers. The low theoretical risk is therefore vastly outweighed by the benefit of screening.

Psychological impact

Participation in screening has a range of psychological impacts, both positive and negative (75). Inducing distress amongst an asymptomatic population is a screening harm, especially when it results from inconsequential findings such as false positives and overdiagnosis. Longitudinal study of trial participants found transient adverse responses among those with concerning LDCT findings, but these did not reach clinical significance or persist long-term (76-80). Whilst the magnitude of this harm appears limited, it is important to minimise any anxiety that may deter high-risk, often socioeconomically disadvantaged and hard-to-reach, individuals from engaging (81). Positive responses to screening have been identified, including empowering otherwise fatalistic smokers to exert control over their health, which could be leveraged to augment the benefit of screening (82).

Incidental findings

The identification of incidental findings on LDCTs presents both challenges and opportunities. Extrapulmonary abnormalities can represent significant disease that would benefit from treatment, such as other malignancies. However, many incidental findings do not represent clinically significant disease, and further investigation of these leads to unnecessary cost and patient harm. Reported rates of incidental findings range from 7% to 46%, partly depending on definitions used (16,83-89). While the optimal strategy for handling incidental findings has been debated (85,90). Pragmatic protocols have been produced to streamline management (91-93). The net impacts of incidental findings on screened populations' health and on the cost-effectiveness of screening programmes are beginning to be evaluated and may be modest (87,89), but these impacts will vary according to scan reporting practices and thresholds for further investigation, so further study is required.

Healthcare resource utilisation

With so many moving parts at all stages of the lung cancer screening pathway, including cancer risk prediction, variation between screening protocols, advancing treatments, and changing costs over time, estimating cost-effectiveness based on available (and ever-ageing) evidence is highly complex and imprecise. Existing estimates of certain protocols show that lung cancer screening is likely to meet cost-effectiveness thresholds in affluent healthcare systems. While the NLST had an incremental cost-effectiveness ratio (ICER) of $81,000 per quality adjusted life year (QALY) gained (94) and the USPSTF 2021 programme estimates $72,564/QALY (95). UK initiatives appear to have more controlled costs, at £8,466/QALY in the UKLS trial and £10,069/QALY in the Manchester pilot (96-98). These estimates are well below the US cost-effectiveness threshold of $100,000/QALY (95) and the UK willingness-to-pay threshold of £20,000–30,000/QALY (99). Furthermore, a preliminary cost-effectiveness evaluation commissioned by the UK National Screening Committee estimates an ICER as low as £1,529 (38).

Additionally, the healthcare infrastructure required for lung cancer screening brings a number of indirect benefits

to the system. Investment in scanning capacity, thoracic radiology expertise, and lung cancer care pathways may benefit many patients who do not participate in screening. Longitudinal imaging over time in a large number of individuals presents an opportunity for research to better understand the natural history of pulmonary nodules, as well as data on which to train machine learning technologies as the field of radiomics and computer-aided reporting develops at pace (100).

Screening programmes can be organised in a variety of ways. Decentralised approaches are based on referral to screening from primary care to diagnostic providers. While this can promote local engagement, standardisation of practice is challenging. Centralised models are led by diagnostic services, encouraging referrals from primary care. Referral rates can be lower, but specialist expertise and quality assurance can be more easily maintained. Hybrid models integrate community services and screening providers, being overseen by a multidisciplinary stakeholder committee. Centralised and hybrid models have been most common in clinical trials and are likely to be favoured for large-scale implementation (101,102).

Surgical considerations

Benign resection

Screen-detected suspected lung cancer brings a multitude of challenges in terms of diagnosis and management. The *bête noire* of screening programmes is the patient who undergoes unnecessary resection for subsequently proven benign disease. All management principles should be underpinned by the need to avoid such a scenario. Although CT-guided biopsy is now routinely performed, such a procedure can be precluded by size and location of the suspected pathology. Emerging options such as navigation bronchoscopy and robotic bronchoscopy seek to further improve rates of tissue diagnosis (103). Nonetheless, it is foreseeable that screening programmes will lead to an increase in the number of patients referred for resection of lung nodules and lesions without pre-operative histological confirmation of malignancy. Thorough discussion at multidisciplinary team meetings is essential, as is robust discussion with patients where the risk of resecting healthy parenchyma without evidence of cancer is emphasised. Emerging bronchoscopic interventions such as radiofrequency and microwave ablation to treat peripheral lung lesions, or brachytherapy or photodynamic therapy for endobronchial lesions, may eventually obviate the need for surgery in a proportion of cases (103).

Considering surgical options, one approach is to undertake a greater number of intra-operative frozen sections. However, this brings with it longer operative times, reduced operating list capacity and greater pressures on histopathology services. Furthermore, particularly for very small lesions and those in difficult to reach areas of the chest, identification of the pathology can be challenging. This is especially true when surgery is undertaken via a minimally invasive approach, and the surgeon relies on either visualising the lesion on the screen or palpating it with a finger through one of the small surgical incisions. Alternative technical solutions to this issue include the use of indocyanine green (ICG). ICG is a dye which emits light when exposed to near-infrared light and has been used in medicine for many years. Within thoracic surgery, its uses include identification of chyle leaks, identification of bullous lesions, delineation of anatomical intersegmental planes and identification of pulmonary nodules (104). Again, whilst it has been proven to be beneficial in terms of aiding identification of small lung nodules, there are cost, technology and training implications which must be addressed if centres intend to adopt its use as part of their routine practice.

Minimally invasive surgery

The proportion of patients undergoing minimally invasive surgery [both video-assisted thoracoscopic surgery (VATS) and robot-assisted thoracoscopic surgery (RATS)] has increased exponentially in recent years (10). Indeed, UK guidelines now advocate that all patients with early-stage lung cancer should undergo minimally invasive resection as the gold standard of care, where anatomically possible (105). Consequently, additional financial investment to augment the capacity of operating centres to support increased numbers of minimally invasive resections will be required. Specialised instruments, cameras and video systems are all essential prerequisites for thoracoscopic surgery in current practice. Taken together with the needs of the broader lung cancer team, new hybrid theatre environments are likely required to support the diagnostic and treatment impact of lung cancer screening.

Parenchymal sparing resections

In recent years, surgeons have started to consider whether sublobar resection, with its associated parenchymal-sparing benefits, can provide similar oncological outcomes

when compared to anatomical lobectomy, traditionally recognised as the gold standard operation for primary lung cancer and supported both by NICE and BTS guidelines as the first line for all suitable patients (49,106,107). The underlying evidence base is mainly derived from the Lung Cancer Surgery Group (LCSG) randomised trial from Ginsberg *et al.* published in 1995. This study demonstrated a superiority for lobectomy over sublobar resections (a subgroup which included both anatomical segmentectomy and non-anatomical wedge resection), for NSCLC ≤3 cm in terms of recurrence rate, with no significant difference in 5-year overall survival (P=0.088) (108). It has been postulated that the lower recurrence rate associated with lobectomy may be attributed to the higher number of intrapulmonary lymph nodes intrinsically provided in the specimen (whilst sublobar resections may simultaneously lead to under-staging of patients with occult nodal disease) and to the more extensive mediastinal lymph node dissection reported with lobectomy in comparison to the sublobar approach (109). Conversely, greater peri-operative morbidity and mortality, in addition to a potentially heavier impact on cardiopulmonary function may be expected with lobectomy, given the more extensive parenchymal resection performed.

Following the LCSG trial, multiple other non-randomised studies have been undertaken, which have, overall, demonstrated a trend towards oncological superiority for segmentectomy over wedge resection (49,110,111) and non-inferiority for segmentectomy compared to lobectomy (111-120). A welcome recent addition to the literature is a study outlining the preliminary results of the JCOG 0802 trial (121). This study randomised 1,106 patients with NSCLC <2 cm to either lobectomy or segmentectomy. Although segmentectomy was associated with a significantly greater proportion of locoregional recurrence, there was no significant difference in overall survival and relapse-free survival between the two groups. There was also a significantly lower reduction in post-operative respiratory function in the segmentectomy group, leading to the study authors suggesting that anatomical segmentectomy should become the standard operation for very small early-stage lung cancers. Of note, more than 90% of tumours included in this study were adenocarcinomas, meaning that application of these findings to other histological subtypes, such as squamous cell carcinoma, should be undertaken with caution. The study is of particular relevance in the context of lung cancer screening where small tumours represent a much greater proportion of the overall caseload. Although not yet formally supported by international guidelines, there is increasingly compelling evidence emerging to support the introduction of anatomical sublobar resections for small tumours to preserve pulmonary function without sacrificing long-term oncological outcomes (122-124).

Lung Health Check (LHC) model

Smokers carry a high burden of comorbidity and early mortality in addition to their cancer risk. Overlapping risk factors such as socioeconomic deprivation mean that they are less likely to access preventive care, further compounding the harms of smoking. As lung cancer screening seeks to engage such a population, it presents an opportunity to offer targeted assessment during an initial 'LHC' consultation and provide high-value interventions to wed prevention to early detection, a model that has been developed and adopted in the UK.

Tobacco dependency

Smoking cessation reduces the risk of developing lung cancer (125). For those who are diagnosed with lung cancer, it is associated with substantially improved overall survival (summary RR 0.71, 95% CI: 0.64–0.80) (126). Interventions to aid cessation are highly cost-effective, particularly varenicline and nicotine replacement therapy, which cost approximately £700 per QALY gained (127-130).

Airways disease

The global prevalence of COPD is estimated to be 11.7% and it is the third biggest cause of death, yet it is grossly underdiagnosed even in affluent countries: a French cohort found an underdiagnosis rate of 70% (131-134). Whilst screening for asymptomatic COPD is not recommended generally, it is an independent predictor of lung cancer risk (OR 2.5) (135,136). Spirometry can be performed alongside lung cancer screening and may help, ultimately, to refine the current risk algorithms. Lung cancer screening studies have identified airways obstruction in 37–45% of participants, 42–50% of whom had no previous diagnosis of COPD (137,138). In the Manchester LHC pilot, 9.9% of the screened cohort had undiagnosed symptomatic airways obstruction (138), a cohort at-risk of exacerbation, hospitalisation and death (139). Identifying symptomatic cases is important to enable sufferers to access the pharmacological and non-pharmacological interventions available to them.

Cardiovascular disease

Many of those at high risk of lung cancer are also at high risk of cardiovascular disease, given their overlapping risk factors. Indeed, more NLST participants died from cardiovascular disease than from lung cancer (25% *vs.* 24%) (140). Cardiovascular risk profiling can be performed using prediction scores (e.g., QRISK2) and coronary artery calcification seen on LDCT. Therefore, it has been proposed that this be assessed on LDCTs performed in lung cancer screening (141). In two UK programmes, approximately half (47–57%) of those with QRISK2 scores ≥10% had not been on statin therapy, despite this being recommended in clinical guidelines (142-144).

Opportunistic assessment for high-prevalence comorbidity during an LHC is an appealing approach which can add to the cost-effectiveness of lung cancer screening programmes (98) and make a substantial contribution to tackling the leading causes of health inequality and the mortality gap between the most and least deprived in society (145).

Conclusions

Lung cancer screening has the potential to greatly increase the number of early-stage lung cancers identified in the UK, which is likely to lead to a significant increase in both the number and proportion of patients with lung cancer undergoing radical surgery with curative intent. Further trials are underway to evaluate and refine screening methods (48,68,92,146), Novel approaches to improve risk prediction are being explored, including blood-borne markers (147-149) and machine learning-assisted image analysis (100). Emerging national projects will provide lessons in service provision in diverse settings. Lung cancer screening prevents deaths, and a major current priority is to improve the identification of those who will benefit the most so that healthcare resources can be focused on them. In parallel with ongoing improvements in prevention (150-153), diagnostics, and treatment, there is cause for optimism that real progress to reduce the burden of lung cancer is feasible. However, the management of screen-detected lung pathology brings additional challenges in terms of diagnosis and management, particularly for small lesions with no pre-operative histological diagnosis of cancer. Contemporary technology, effective patient prehabilitation, a minimally invasive surgical approach, and minimising the amount of lung parenchyma resected are emerging as key concepts in this area of lung cancer surgery. Long-term follow-up of patients already participating in screening trials is expected to inform robust guidelines to support the management of these patients.

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