Low-dose CT screening: the (other) lung cancer revolution

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The advent of immune checkpoint inhibitors for the treatment of metastatic non-small cell lung cancers has been a bright spot in the otherwise-bleak landscape of the UK's deadliest cancer. In a disease where two thirds of those who present with a new diagnosis will be dead within a year, and survival outcomes have changed little in the last four decades (1), the potential to extend progression-free and overall survival by on average 4 months (2) is noteworthy. Immunotherapy may play a starring role in the future of lung cancer treatment but there is a more revolutionary approach to improving lung cancer outcomes: low-dose CT (LDCT) screening. Lung cancer screening (LCS) with LDCT demonstrates considerable lung cancer and all-cause mortality risk reduction (3,4). LCS and effective and embedded smoking cessation interventions show synergy, with the mortality reduction of screening essentially doubled by prolonged cessation (5). However when it comes to LDCT screening, there is still a hearts-and-minds battle to be won.

Evidence (and Reticence)

LDCT screening for lung cancer arrived in 2011, with the publication of the National Lung Screening Trial's (NLST) mortality results: the large American trial (n=53,454) demonstrated that, compared to annual chest radiograph, LDCT screening reduced lung cancer mortality by 20%, and all-cause mortality by 7%(3). Smaller studies in the UK have reinforced the benefits of LDCT screening, demonstrating a stage-shift of disease to stages I and II when screening is performed in high-risk populations(6,7). Early mortality data from the NELSON trial (n=15,822) demonstrates a 26% lung cancer mortality risk reduction in men screened with LDCT, compared to standard of care (no screen); the reduction may be even greater in women(4).

In February 2019, as part of the NHS Long Term Plan, it was announced that more lung health checks and same-day LDCT scans would be offered to those at

highest risk of lung cancer (8). These lung health checks will take the form of ten discrete pilot schemes in the areas of England with the worst lung cancer outcomes(9). However the UK National Screening Committee (NSC) is yet to endorse a national lung cancer screening programme, and until it does, provision of LDCT screening will be limited to pilots and research studies, meaning many lives that could be saved will be lost.

The NSC must assess the evidence of efficacy and determine the health economics of such a new service, as well as working with the government and Royal Colleges in managing infrastructure and workforce implications. Alternatively LDCT may not fulfill the criteria to be assessed by the NSC. This seems odd, after all it is called LDCT *screening* across the world. However, there is the suggestion that LDCT screening is simply 'early diagnosis in a high-risk cohort'. If the NSC decides not to assess LDCT screening then the work will fall to NICE; meaning, if approved, there would be no national programme but rather locally implemented efforts in delivery, similar to the current situation in the US.

Challenges to LCS

The UK LCS community has three specific challenges to address, summarised by Wilson and Jungner over half a century ago. First "to bring to treatment those with previously undetected disease [uptake]", second "to avoid harm to those persons not in need of treatment [minimising harms]" and third, to ensure that "the cost of case-findings (including diagnosis and treatment) … be economically balanced in relation to possible expenditure on medical care as a whole [cost-effectiveness]" (10).

In terms of uptake, 'apathy' in smokers and ex-smokers about their health has been raised as a barrier to effective engagement. In the US, where LDCT screening is paid for by state-sponsored Medicare and Medicaid programmes, uptake has been inconsistent: it is estimated that only 4% of those eligible have undergone screening (11,12). This disappointing response is a result of the provision of healthcare, relying on family practitioners being aware of LCS screening—many are not—and having access to centres that provide it (11).

Importantly, the evidence from UK screening studies and pilot programmes demonstrate a more positive picture when LDCT screening is approached with a systematic, population-based invitation strategy. Initial figures from the Lung Screen Uptake Trial in London demonstrate that when high-risk populations identified in primary care databases are approached with an invitation from their GPs to participate in a lung health check, response rates are over 50% (13).

The second challenge is perceived harms to those screened, specifically over-diagnosis (where a true cancer is identified that would not have harmed that person in their lifetime); false positive results, where unnecessary investigations or interventions are undertaken for a person who does not, ultimately, have a cancer; and the (over)management of incidental, non-lung cancer findings, which may or may not have caused the individual harm if left undetected.

The initial estimate of over-diagnosis in NLST was 18.5% (measured 6 years from trial entry) (14). However, with longer follow up (up to 12 years), rates dropped considerably to 3.1%. Interestingly rates of over-diagnosis remained high (79%) for broncho-alveolar cell carcinomas (15). These lesions, now largely referred to as adenocarcinoma in situ, tend to correspond to pure ground glass nodules (pGGN) on CT scans; contemporary strategies encourage surveillance only, reflecting their very indolent course. For context, breast screening quotes an overdiagnosis rate of 19% (16).

Reported rates of false-positive screens vary considerably. The NLST published a rate of 23.3% (centres in the US have reported rates as high as 58% (18)); UK Lung Screening trial (UKLS) and NELSON both quote 3.6%. This variability reflects different definitions of 'positive findings': e.g. in excluding nodules that require a repeat scan in 3-months' time, the rate of 'false positives' (and associated harms) reduces substantially. Only those nodules of size-significance, increasing growth or changing morphology are invasively investigated.

LDCT screening also requires a unified approach when it comes to incidental findings; unlike in breast or bowel screening, where only the target area is

imaged, LDCT screening captures the entire thoracic cavity. Recommendations for further investigation or management should be evidence-based in order to prevent unnecessary and unhelpful intervention (17), while providing the best possible outcomes for patients. Data gathered from LDCT trials currently underway in the UK will go some way to providing support for comprehensive guidelines.

Yes, but is it worth the cost?

Having maximized participation and minimized harms, the final challenge is demonstrating the cost-effectiveness of screening and justifying the very considerable investment required to set up a comprehensive UK-wide screening programme whilst the NHS struggles with a limited budget and ever-increasing demands on existing services.

There has been, to date, no published estimate of the likely total cost of a nationwide lung cancer screening programme, but informal estimates have ranged from £100 to £200m per annum. Analysis from the Health Economics Unit at York University allows an estimation of these opportunity costs (18). A lung cancer screening programme costing between £100m and £200m may result in the loss of between 2,330 and 4,659 life years (and 7,733 and 15,465 QALYs) elsewhere in the NHS(19). There would need to be clear demonstration that the expected gains from LCS justify this displacement of resource. Cost effectiveness analyses from both the UK Lung Screening Pilot and the Manchester Lung Health Check programme demonstrate favorable incremental cost effectiveness ratios (ICERs), where the anticipated gains would clearly exceed the opportunity costs described above (6,20). A modeling study produced for the Health Technology Authority demonstrated a cost-effectiveness assessment less favorable and closer to the supposed “NICE threshold” (21). However, this analysis pre-dated publication of both the NELSON results (showing a greater reduction in mortality than NLST) and more mature data from NLST demonstrating low rates of overdiagnosis. Re-evaluation of cost-effectiveness incorporating the latest data is required.

It is frequently commented that consideration of a national screening programme whilst the UK as a whole disinvests in smoking cessation interventions (the annual spend on smoking cessation services in England reduced from £128 million in 2013/14 to £89 million in 2017/18 (22)) makes little sense. Smoking cessation interventions represent one of the most cost-effective interventions in the whole of healthcare, and there is therefore urgent need to reinvest in these services. However, to use this disinvestment as a reason not to fund a Lung Cancer Screening programme seems perverse. The close link between smoking cessation and lung cancer screening offers an opportunity to embed one within the other, improving the cost-effectiveness of the overall bundle of activity. Modelling studies that project doubling of smoking cessation rates through the screening episode, show a halving the ICER (23). Delivering smoking cessation interventions co-located with lung cancer screening is being pursued in many of the UK Lung Health Check programmes.

LCS and the Future

With two large randomised trials demonstrating reduced lung cancer mortality, and newer data demonstrating significantly lower harms than originally reported, the arguments in favour of LCS at a participant level are difficult to ignore. Debate will continue about the health economic assessment of LCS and whether this represents value for money. Much will depend on the risk threshold at which people are invited for lung cancer screening. The higher the lung cancer risk required to enter a screening programme, the greater the yield of cancer (per person screened) and the more cost-effective a programme would be. Yet by limiting LCS to a higher-risk cohort, the overall number of cancers detected and therefore lives saved would be reduced. Ongoing studies comparing risk thresholds will be critical in informing this debate.

The UK National Screening Committee is optimally placed to make these assessments, and provide the infrastructure required for any possible future nationwide programme. Only with the rigour of data collection and quality assurance alongside workforce expansion and training, can we be assured that the impressive results from screening studies be replicated in centres across the

country. Without such an approach, we may face another postcode lottery of implementation, and miss out on the considerable benefits that LCS has to offer. With immunotherapy extending life after diagnosis for those with late-stage disease, a comprehensive high quality LDCT screening programme preventing many people from reaching late-stage disease, and smoking cessation embedded at all steps of the pathway, we may finally start to see a turnaround in lung cancer outcomes.

Study	Recruitment Period	Recruitment Criteria	Screening Methods	Sample size (number screened)	Nodule threshold	Mortality Benefit	Cancer Detection Rate
NLST (3)	2002-2004	Age 55-74, ≥30PY, quit<15 years ago	Annual LDCT or CXR for 3 years	53454 (26722)	4mm	20% RR LCM 6.7% RR ACM	1.0%
MILD (24)	2005-2011	Age>49, ≥20PY, quit<10 years ago, no recent cancer within last 5 years	3 groups- no screen vs. annual LDCT vs. biennial LDCT for 5 years	4099 (2376)	60mm^3	Yes (NS) 30% RR LCM 17% RR ACM	0.7%
ITALUNG (25)	2004-2006	Age 55-69, ≥20PY	Annual LDCT for 4 years vs. no screen	3206 (1406)	5mm	Yes 39% RR LCM 20% RR ACM	1.4%
DANTE (26)	2001-2006	Age 60-75, ≥20PY, quit<10 years ago, male	Annual LDCT for 4 years vs. no screen	2472 (1276)	5mm	No	2.2%
DEPISCAN (27)	2002-2004	Age 50-75, ≥15PY	Annual LDCT vs. annual CXR for 2 years	765 (336)	5mm	Not reported	2.4%
DLCST (28)	2004-2006	Age 50-70, ≥20PY, quit<10 years ago, FEV1>30%, able to climb 2 flights of stairs, excluded if recent cancer/ terminal illness	Annual LDCT vs. usual care for 5 years	4104 (2052)	5mm	No	0.8%
NELSON (29) (4)	2003-2006	Age 50-75, ≥15PY	LDCT screen at 0, 1, 3 & 5.5 years vs. no screen	15822 (7155)	50mm^3	Yes 26% RR LCM (men) 39% RR LCM (women)	0.9%
UKLS (30)	2011-2013	Age 50-75, ≥5% 5 year lung cancer risk as calculated by LLPv2 score	Single LDCT screen vs. no screen	4061 (1994)	≥15mm^3/ 3mm: 12 month scan. ≥50mm^3: 3 month scans	Not reported	2.1%

Table 1: Summary of Randomised LCS Studies. Adapted from M Ruparel, 'Implementing CT Screening in the UK: finding an evidence base for practical strategies' (31).

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