Screening for lung cancer by low-dose CT

The past 15 years have seen improvements in survival from breast, prostate and colorectal cancer, but lung cancer has continued to lag behind. One of the major difficulties is that most of the time it is incurable at diagnosis. This led to growing interest in screening high-risk individuals by low-dose CT.
There is a growing body of evidence to suggest this is a useful intervention. Before we consider the evidence, let's look at what is happening in the UK already.

The Targeted Lung Health Checks Programme

Lung cancer screening works and has been implemented in the USA.

There is no nationwide lung cancer screening programme in the UK…yet. But case-finding 'Lung Health Check' schemes are taking place at 14 sites across the UK, and may be happening in your area.

These follow on from a successful pilot of the Lung Health Check Programme in Greater Manchester (Thorax 2018;doi: 10.1136/thoraxjnl-2017-211377).

In this pilot, patients aged 55–74y at 14 practices were invited to book an appointment if they were current or ever smokers but did not have a diagnosis of lung cancer or another terminal illness.

2500 people attended an appointment with a specialist nurse in a supermarket car park. On-site, low-dose CT was offered to those identified as being 'high risk' by the assessment. Risk status was determined by a number of factors including current smoking status, pack-year history, spirometry indicative of COPD and presence of symptoms; these were input into a computer model, with 'high risk' defined as a 6-year risk of lung cancer >1.5%.

The outcomes were:

- Just over 50% of participants were found to be 'high risk' and they went on to have low-dose CT screening.
- Of the 1500 individuals screened, 46 participants were found to have lung cancer; 80% were at stage 1, with 65% suitable for surgical resection.

With thanks to GPCPD Red Whale

- **One lung cancer was diagnosed for every 33 people screened as a one-off intervention.**
- This pilot was not designed or powered to look at subsequent morbidity and mortality.

Following this, in February 2019, NHSE announced a £70 million investment in a similar model to be rolled out across 10 English Cancer Alliance areas over the next 4 years, with 14 sites proposed. In addition, the very large SUMMIT study has started in London; it aims to recruit 50 000 people into a lung cancer screening programme which will combine low-dose CT with an innovative blood test (BJGP 2019;69(679):90).

What is the evidence?

The largest and best designed RCT of low-dose CT lung cancer screening is the large US National Lung Screening Trial (NLST NEJM 2011;365:395). Entry criteria was smokers with a 30 or more pack-year history, and they were randomised to annual low-dose CT or chest radiograph screening. Follow-up was for 7 years. This trial showed significant benefits of low-dose CT screening:

- 20% (CI 6.3–26.7%) reduction in lung cancer mortality.
- 6.7% (CI 1.2–13.6%) reduction in all-cause mortality.
- 24% of participants screened 'positive' for nodules on their first CT; the vast majority (96%) were false positives. These nodules then need follow-up.
- This means that 320 people had to be screened by one-off low-dose CT to prevent one lung cancer death.

This compares favourably with colorectal and breast screening. Smaller European studies showed similar but less powerful results, and this, along with concerns about overdiagnosis and cost effectiveness, has probably led to slower uptake across Europe.

However, the 'NELSON study', a further large, European RCT study, randomised more than 15 000 predominantly male current or past smokers to screening with 4 CT scans over 10 years vs. no screening. It demonstrated a significant lung cancer mortality benefit, and this is probably largely attributable to lung cancers being detected at a much earlier stage. Despite more than 80% of participants being male, the greatest benefits were seen in the female cohort. It was not powered to detect a difference in all-cause mortality. By 10 years, the maximum rate of over-detection was thought to be no more than 9%, and this was considerably less than lives saved.

The number needed to screen with 4 CTs over 10 years was 131 to prevent 1 cancer death (NEJM 2020;382:503).

The accompanying editorial concludes, "there can no longer be any doubt as to the efficacy of periodic low-dose CT screening in reducing mortality from lung cancer". The remaining

With thanks to GPCPD Red Whale

challenges are assessing cost effectiveness and the best protocol to best identify the target population, maximise benefit and minimise overdiagnosis.

Overdiagnosis

The overdiagnosis rate in the US National Lung Screening Trial was subsequently estimated to be 18.5%, with pulmonary nodules being the main cause of a false positive result. The NELSON study used a different protocol to assess nodules and, by the end of the 10-year follow-up period, the overdiagnosis rate was reduced to a maximum of 9%.
The assessment and risk stratification of nodules matters because of the potential radiation exposure involved in follow-up.

Radiation exposure

A single low-dose CT is a similar dose of radiation to a mammogram.
The challenge comes for patients who are identified as having lung nodules and who would be offered *annual* low-dose CT. For these patients, a recent study evaluated the impact of radiation exposure for those undergoing annual CT for 10 years, and estimated that (BMJ 2017;356:j347):

- For every 100 cancers detected earlier, 1 radiation-induced cancer will be caused.
-

Cost effectiveness

The pilot phase of the largest UK-based RCT for lung cancer screening estimated that the cost was around £8500 (CI £5542 to £12569) per quality-adjusted life year gained (Thorax 2016;71:161;doi.10.1136).

With thanks to GPCPD Red Whale