LUNG CANCER

Screening for lung cancer using low dose CT scanning

R MacRedmond, P M Logan*, M Lee, D Kenny, C Foley, R W Costello

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See end of article for authors' affiliations

Correspondence to: Dr R MacRedmond, Department of Respiratory Research, Education & Research Centre, Beaumont Hospital, Dublin 9, Ireland; rmacredmond@rcsi.ie

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Background: Lung cancer is the most common cause of cancer related death in Ireland. The majority of lung cancers are inoperable at the time of diagnosis and consequently the overall 5 year survival is less than 10%. The objective of the ProActive Lung Cancer Detection (PALCAD) study was to evaluate whether low dose chest computed tomographic scanning (LDCCT) can detect early stage asymptomatic lung cancer in a high risk urban population.
Methods: Four hundred and forty nine subjects of median age 55 years (range 50–74) with a median pack year smoking history of 45 years (range 10–160), with no previous cancer history and medically fit to undergo thoracic surgery were recruited. After informed consent, LDCCT was performed on all subjects. Non-calcified nodules (NCNs) of ⩾10 mm in diameter were referred for biopsy. Follow up with interval LDCCT at 6, 12 and 24 months to exclude growth was recommended for NCNs <10 mm in diameter.
Results: Six (1.3%) NCNs of ⩾10 mm were detected of which one (0.23%) had non-small cell lung cancer stage 1; 145 NCNs of <10 mm were detected in 87 (19.4%) subjects. Mediastinal masses were detected in three subjects (0.7%)—one small cell lung cancer and two benign duplication cysts. Incidental pathology was noted in 276 patients (61.5%), most commonly emphysema and coronary artery calcification.
Conclusion: The prevalence of resectable lung cancer detected by LDCCT at baseline screening was low at 0.23%, but there was a high rate of significant incidental pathology.

Lung cancer is the most common cancer in the world[1] and is the commonest cause of cancer related death in Ireland, accounting for 20.3% of all such deaths.[2] While lung cancer rates in Irish men are similar to the European average, they are 66% higher in women than in other European countries.[2] Overall, the survival rates for patients with lung cancer are very poor with the 5 year survival ranging from 5.5% to 14% across Europe.[3 4] In Ireland only 10% of men and 8.5% of women are alive 5 years after diagnosis.[2] Audits of patients presenting with lung cancer to UK and Irish hospitals have shown that, at the time of diagnosis, approximately 70% of cases are at an advanced stage (stage 3B or 4).[5 6] The fact that most patients present at a late stage, combined with smoking related co-morbidity that can render patients unsuitable for surgery, means that only 15% of lung cancer patients in Ireland proceed to surgery.[2] Early diagnosis, however, can improve survival. For example, 5 year survival rates after resection of stage 1 lung cancer of over 70% can be achieved, with 5 year survival rates after resection of stage 1A cancers less then 20 mm of over 90%.[7 8] This compares with survival rates for stage IV disease of <3%.[2] A screening programme for high risk individuals resulting in earlier diagnosis and intervention may therefore improve survival.

Early screening studies using chest radiography and sputum cytology as the screening modalities failed to achieve any significant reduction in lung cancer mortality.[9–12] This failure has been attributed partly to problems with study design, in particular flawed randomisation and screening contamination of control groups, but may also be due to the poor sensitivity of chest radiography in detecting small tumours.[13] The development of low dose spiral chest computed tomographic (LDCCT) imaging has resulted in a resurgence of interest in screening for lung cancer. A retrospective study of histologically confirmed non-small cell lung cancers showed that the cancer was not visible on the chest radiograph in 19% of cases,[14] while comparative studies have shown that chest radiography misses up to 77% of tumours detected by LDCCT.[15 16] This suggests that LDCCT may be a more sensitive screening tool for small tumours. Initial reports from non-randomised screening programmes of smokers using LDCCT were very encouraging. The Early Lung Cancer Action Project (ELCAP) study from New York reported a prevalence rate for CT detected lung cancer of 2.7% in 1000 current or ex-smokers aged over 60 years, 85% of which were stage 1. Benign intervention rates were low at 1/28.[17] The prevalence of lung cancer in Ireland is similar to that in the USA,[1] but the 5 year survival rates are even lower than their disappointing rate of 14%.[18] Applying a similar study design, we examined whether the high rate of detection of resectable cancers reported in the ELCAP study[17] could be reproduced in our local population.

The principal objective of the ProActive Lung Cancer Detection (PALCAD) study was to evaluate whether LDCCT is useful in detecting asymptomatic lung cancer in a high risk population in an urban setting.

METHODS

The study design was approved by the international ELCAP review process, an initiative set up by the Cornell group[17] to help other institutions in planning lung cancer screening studies. The study protocol was approved by the hospital ethics committee and all patients gave informed consent before enrolment.

Enrolment

Residents of the community of 300 000 people served by our hospital aged 50 years or over with a history of at least 10 pack years smoking and still smoking at the age of 45 with no prior history of cancer and medically fit for thoracic surgery were offered lung cancer screening by local media advertising. Patients were deemed medically fit if they had no chronic medical conditions that would preclude them from surgery, were not oxygen dependent, and could breath hold for 20 seconds.[17] All potential recruits were interviewed by

*On behalf of the ProActive Lung Cancer Detection (PALCAD) investigators.

the study coordinator to ensure suitability for investigation or treatment and to record demographic details as well as age, smoking habits, exposure to asbestos, and prior medical history.

Screening test

At baseline, spiral 10 mm, pitch 2, low dose (50 MA or less) CT images were obtained from each participant and reconstructed using a high resolution algorithm in overlapping 5 mm increments. All images were acquired using the same scanner, a Siemens (Erlanger, Germany) Emotion single slice helical CT scanner.

The CT scans were independently evaluated by two radiologists. Particular attention was given to the presence of pulmonary nodules/masses or regions of ground glass attenuation. Other parenchymal, mediastinal, pleural, and extrathoracic abnormalities were recorded. If the findings of the two radiologists did not concur, the scans were jointly re-evaluated and consensus findings were documented. The defined characteristics of any nodules detected on LDCCT scans were recorded. This included the nodule size (mean length and width), shape (round if width to length ratio was <2–3, otherwise non-round), location (lobe and distance from pleura, central if more than 2 cm from pleura), margin (smooth, non-smooth), and the presence or absence of benign calcification.[19]

Criteria for intervention

Where LDCCT detected a nodule, a standard staging CT scan was obtained with a high resolution CT (HRCT) image through the nodule to look for previously undetected benign-type calcification. If the criteria for benign calcification were not met,[19] nodules were investigated as shown in fig 1. A non-calcified nodule (NCN) of ⩽5 mm in diameter was followed up by HRCT scanning at 6, 12, and 24 months unless growth was found on one of the intervening scans. Nodules followed without change in this manner for 24 months were considered to be benign. NCNs 6–10 mm in diameter were considered suitable for biopsy depending on their location and other characteristics. Biopsy (video assisted thoracotomy (VATS) or percutaneous) was recommended for nodules with characteristics highly suspicious of malignancy. If a biopsy was not recommended or feasible, follow up was as for nodules of ⩽5 mm diameter. Patients with nodules of ⩾11 mm diameter were referred to a pulmonary physician with recommendations to proceed to biopsy. The outcome was recorded by the study investigators

Cases of focal ground glass opacity were treated with broad spectrum antibiotics according to the ATS guidelines for the treatment of community acquired pneumonia[20] and a repeat HRCT scan was performed 8–10 weeks later (fig 2). Focal ground glass opacities that had not resolved after antibiotic treatment were treated as NCNs. Where partial resolution was observed, cases were followed with serial HRCT scans to ensure complete resolution.

All cytological and histological findings from biopsy and surgical specimens were recorded. When a cancer was diagnosed, patients received standard care including tumour staging and appropriate treatment. Incidental findings were evaluated by one of the study physicians, discussed with the patient and primary care physician and, where appropriate, referred for specialist evaluation or further diagnostic testing. Smoking cessation was recommended and facilitated for all patients and influenza/pneumonia vaccination recommended for those with chronic pulmonary disease.

Data analysis and statistics

Data were recorded on an Excel spreadsheet. Analysis was performed using Prism Software, Version 3 (Graph Pad Software, CA, USA). The results are presented as mean, median and ranges.

RESULTS

The baseline demographic characteristics of the 449 volunteers enrolled in the study are shown in table 1. The median age at the time of screening was 55 years (interquartile range (IQR) 52–60). The median number of pack years smoked was 45 years (IQR 35–70). Thirty four patients (7.6%) reported occupational exposure to asbestos, while a further 24 (5.3%) reported household or other exposure felt not to be significant. Even among the occupational exposure group it was impossible to quantify accurately or to verify the duration and extent of asbestos exposure, so these data are felt to be unreliable.

On the initial LDCCT screen six of the 449 patients (1.3%) had NCNs measuring >10 mm (table 2). Percutaneus biopsy was refused by one patient, one had a histological diagnosis

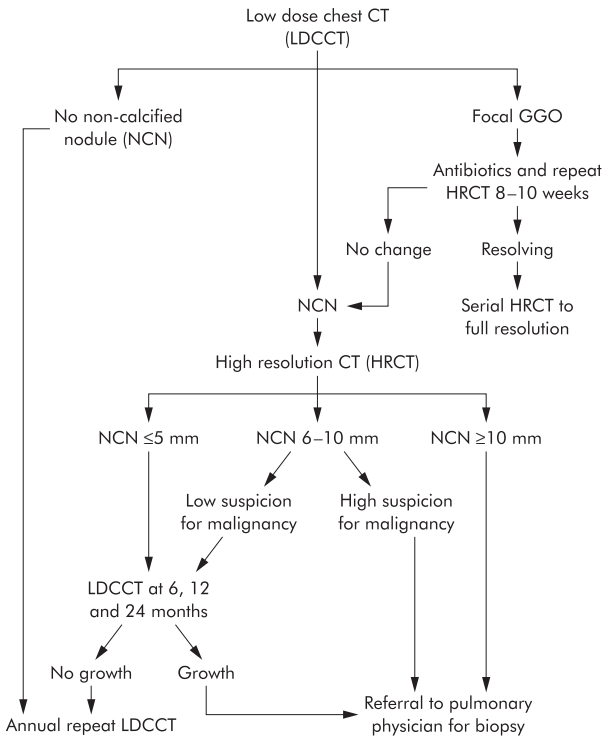

Figure 1 Investigation algorithm for non-calcified nodules (NCNs) detected on low dose chest computed tomographic (LDCCT) scanning.

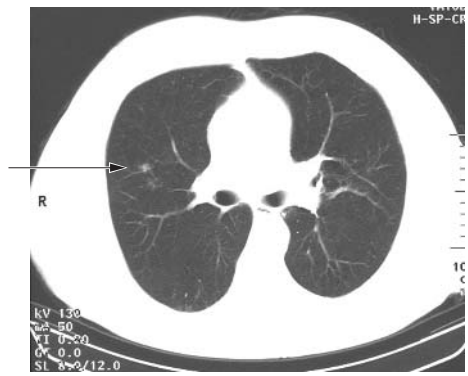

Figure 2 Low dose chest CT scan showing two areas of focal ground glass opacity in the right upper lobe. These were resolved on repeat imaging after antibiotic treatment.

Table 1 Baseline characteristics of the study population (n = 449)

	Number
No of men	224 (49.9%)
Age	56.4 (50–74)
Patients aged >60 years	114 (25.4%)
Pack years smoked	53.4 (10–160)
Number of current smokers	307 (68.4%)
Years since stopping smoking	4.7 (0.3–21)

Data are presented as number (%) or mean (range).

of non-small cell lung cancer and proceeded to lobectomy, and one NCN had resolved on presentation for biopsy. The remaining three had benign cytology on percutaneous biopsy. Of these, one NCN is stable in size at 4 month follow up, one patient dropped out of the study, and the remaining patient's physician recommended thoracotomy which confirmed benign hamartoma.

Mediastinal masses were detected in three patients (0.7%). One patient had small cell lung cancer confirmed at mediastinoscopy while the remaining two were benign duplication cysts (one mediastinoscopy, one MRI).

A total of 145 nodules <10 mm were detected in 87 (19.4%) patients. Eighty four of the 87 patients have had at least one interval scan and none has demonstrated interval growth. Of the remaining three, one died (pancreatic cancer) and two refused repeat scanning and defaulted from the study.

At the initial screen incidental findings were seen in 276 patients (61.5%, table 3). The most common incidental findings were emphysema (29.0%) and coronary artery calcification (14.3%). Significant incidental disease was seen in 221 patients (49.2%) patients. Incidental findings were deemed significant if they required further evaluation or had clinical implications. Significant non-pulmonary disease (other than coronary artery calcification) was seen in 32 patients (7.1%). Cigarette related incidental disease was seen in 186 individuals (41.4%), accounting for 67.4% of all incidental diseases.

Table 2 Number (%) of non-calcified nodules (NCNs), focal ground glass opacities (GGOs), and mediastinal masses found on the initial LDCCT screen

No with NCNs	93 (20.7)
Total number of NCNs	155
NCN ≥10 mm	6 (1.3)
NSCLC stage 1	1 (0.2)
NCN 5–9 mm	68
NCN ≤5 mm	80
Focal GGO	13 (2.9)
Mediastinal mass	3 (0.7)
Small cell lung cancer	1 (0.2)
Benign cyst	2 (0.5)

Table 3 Incidental findings found in 276 abnormal CT scans

Incidental findings	No (%)
Emphysema	130 (29.0)
Mild	68 (15.1)
Moderate	41 (9.1)
Severe	21 (4.7)
Bronchiectasis	44 (9.8)
Coronary artery calcification	64 (14.3)
Idiopathic pulmonary fibrosis	6 (1.3)
Focal inflammation	11 (2.5)
Pleural plaques	4 (0.9)
Goitre/thyroid nodule	9 (2.0)
Thoracic aneurysm	1 (0.2)
Abdominal findings	46 (10.2)
Benign hepatobiliary/renal disease	41 (9.1)
Benign oesophageal thickening	3 (0.7)
Fundal mass	1 (0.2)
Active endometriosis	1 (0.2)

The values are the numbers of individual abnormalities and the percentage represents the proportion of the total study population with an individual abnormal finding. Non-significant findings such as calcified nodes and parenchymal scars are not included.

DISCUSSION

The principal findings of this study were that the prevalence of lung cancer detected by LDCCT in a population of asymptomatic high risk smokers at baseline screening was 0.46%, and the prevalence rate of tumours suitable for curative surgical therapy was 0.23%. This was a disappointingly low yield of lung cancer using LDCCT in a high risk population.

It has already been shown that it is impossible to transport the results of screening in one population to another population in another country. The ELCAP study reported a prevalence of CT detected lung cancer of 2.7%.[17] Subsequent studies published from the USA, Germany and Japan using roughly similar intervention algorithms have failed to emulate the detection rates of the ELCAP study, reporting lower prevalence rates of 1.1–1.7% in high risk populations.[21–23]

It is also important to define the optimum characteristics of a screening population. This study was designed in a similar manner to the ELCAP study reported by Henschke and colleagues and was in line with the study protocol of their international study group. While the mean age at diagnosis of lung cancer in Ireland is 71 years for men and 70 years for women,[24] 22.3% of lung cancer cases in our institution occur in patients aged less than 60 years so a younger lower age limit was chosen. The resulting younger age of our cohort may explain, at least in part, the lower rates of detection of lung cancer in this study compared with others. For example, although both study groups had similar levels of exposure to cigarette smoke, our study population was on average a decade younger than the cohort screened by Henschke *et al* (median age 55 years *v* 67 years). Subgroup analysis of subjects aged over 60 showed that, while the overall nodule detection rate was similar at 19.3%, both patients with lung cancer were aged over 60 years, giving a lung cancer prevalence rate of 1.75% in this older cohort. These data suggest that, if there is a benefit for lung cancer screening with LDCCT, it may not be appropriate in younger smokers.

In previous studies 15 of 27 malignant nodules detected in the Cornell study[17] and six of 25 detected in the Mayo Clinic cohort[21] were less than 11 mm in size. In order to avoid a high number of benign interventions, biopsy specimens were taken only when documented growth was observed at 3 monthly follow up scans in these studies. In our study none of the smaller nodules was deemed highly suspicious for malignancy and all had interval scanning rather than immediate biopsy. Although interval scanning was performed at 6 months rather than 3 months as in the other studies, it is reassuring that 84 of 87 patients with smaller nodules have been re-scanned and none has shown interval growth to date. These nodules will be followed for a full 2 years before being deemed benign. These findings support a less aggressive follow up policy than that used in the two American studies.[17 21]

The overall prevalence of nodules (19.3%) was also lower than in other studies (23–51%).[17 21–23] While the very high

rates in the Mayo Clinic cohort[21] may be at least partly explained by the high rates of endemic fungal granulomatous disease in that area, the German group reported nodules in 43% of participants with very similar demographic characteristics to those of our patients.[22] The collimation differences between the current study (10 mm) and the above mentioned studies (5 mm), and some reduction in sensitivity with film versus workstation viewing may explain the difference in nodule detection rates.

Eight invasive procedures were carried out in seven patients with benign disease (1.6%): three percutaneous lung biopsies, one thoracotomy, one mediastinoscopy, two gastroscopies, and one percutaneous biopsy of an abdominal mass. These data indicate that there was a high incidence of intervention in our study group for a wide range of benign conditions. Of the two nodules removed at surgery, one was a non-small cell lung carcinoma while the other was a benign hamartoma. This contrasts sharply with the frequently quoted low rates of benign intervention in the ELCAP study[17] in which only one of 28 biopsy specimens yielded benign disease and there were no thoracotomies for benign disease. The very high ''benign thoracotomy'' rate in our study is partly due to the low overall prevalence of malignant nodules, but other studies report rates of surgery to remove benign nodules of up to 20%.[22 25] This compares with data from Europe and the US showing that 50% of nodules removed surgically in routine clinical practice are benign[26] but, given the potential morbidity and mortality associated with thoracic surgery, this degree of intervention for false positive nodules may be unacceptable in the context of a mass screening programme.

The success of any screening programme relies on compliance. At the original interview the study coordinator explained the study outline in detail before the patients gave their consent. Unfortunately, two of six participants in whom further intervention for suspicious nodules was recommended refused follow up. One could not be further contacted after withdrawing from the study, while the other reported ''I'd rather not know'' as the reason for refusing further investigation. While it is difficult to make definitive statements based on the behaviour of one individual, this sentiment may reflect a generally fatalistic outlook on lung cancer survival after diagnosis. Of the 87 patients with smaller nodules, only two (2.3%) have declined interval scanning. The high default rate in the ''suspicious for malignancy'' group is a major limitation of our study, but also represents a practical concern in any screening programme.

A higher number of ''incidental'' findings was recorded in our study population than was anticipated. All of these 276 patients were reviewed by their primary care physicians and direct referral to a pulmonary physician was indicated for 25 of 200 patients who had significant pulmonary pathology on LDCCT scanning, mainly severe emphysema, bronchiectasis, or pulmonary fibrosis. Cardiac evaluation was recommended for 64 patients with coronary artery calcification, which is recognised as a surrogate marker of coronary atherosclerosis.[27] Unfortunately, calcium scoring could not be performed on study patients because the CT scans were performed on a single slice CT scanner.

Abdominal disease was detected in 46 patients (10.2%), of whom 19 (4.2%) required further diagnostic evaluation and all were found to have benign disease. One participant died of pancreatic cancer during the study period, but this area was not scanned on his original LDCCT. In contrast, Swensen *et al* found non-pulmonary malignancy in 7.9% of participants.[21] Including pulmonary nodules, 268 participants (59.7%) had a finding on baseline CT scanning that required further therapeutic or diagnostic intervention. After 3 years of scanning Swensen *et al* reported that nearly 80% of participants had one or more findings requiring further diagnostic testing.[25]

While not included in the original study design, the investigators felt a responsibility towards participants not only to inform them of all documented pathologies but also to offer follow up where indicated. While it can be argued that these ancillary findings may save additional lives and thus enhance the value of the screening test,[28] they also contribute to patient anxiety and possibly morbidity through invasive investigations. The finding of high rates of abdominal malignancy in the Mayo study has not been matched by this study, although 19 patients required further investigation to confirm benign disease as a result of LDCCT abnormalities. The recommendation of influenza and pneumonia vaccination for patients in whom chronic pulmonary disease is identified should reduce morbidity, but unless patients are further motivated to stop smoking it is unlikely that identification of these pathologies will have an impact on mortality.[29 30]

The estimated cost of one LDCCT ranges from 50 to 200 euros[22 23] and projected costs of population screening are enormous.[31 32] The additional cost generated by significant incidental disease, as occurred in 49.2% of volunteers in our study, was considerable in terms of both diagnostic and therapeutic intervention. This should be factored in to economic projections for further studies and would obviously have major implications in financing a population based screening programme.

The role of low dose spiral CT scanning in screening for lung cancer remains contentious. Despite initial optimism, concerns remain regarding the high false positive and benign intervention rates which may result in unacceptable morbidity and patient anxiety.[26 33] Whether the observed prevalence rates of early stage cancers will translate into real reductions in mortality or will be confounded by the effects of lead time bias and overdiagnosis remain to be seen.[13] Our baseline data, with considerably lower detection rates and higher rates of invasive intervention for benign masses, suggest a note of caution in the implementation of mass screening programmes for lung cancer, at least in younger patients, and compound the need for large scale randomised controlled trials. In addition, these data highlight the considerable additional costs, with as yet unproven additional benefit, generated by the high rates of ancillary disease.

Authors' affiliations

R MacRedmond, R W Costello, Department of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland
P M Logan, M Lee, Department of Radiology, Royal College of Surgeons in Ireland, Dublin, Ireland
D Kenny, C Foley, Clinical Research Centre, Beaumont Hospital, Dublin, Ireland

The PALCAD investigators comprise the authors and Dr E Kay, Professor M Leader, Mr P Broe, Professor C Kelly, Dr L Grogan, Professor S O'Neill, and Professor N G McElvaney.

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LUNG ALERT

Does oestrogen lead to improved survival in women with non-small cell lung cancer?

▲ Moore KA, Merry CM, Jaklitsch MT, *et al*. Menopausal effects on presentation, treatment, and survival of women with non-small cell lung cancer. *Ann Thorac Surg* 2003;**76**:178–95

Previous reports have shown higher survival rates in women than in men with non-small cell lung cancer (NSCLC), and oestrogen receptors are expressed on human NSCLC cells. 14 676 women from the US 1992–1997 Surveillance, Epidemiology, and End Results database with primary NSCLC were categorised as premenopausal (age 31–50 years, n = 2230) or postmenopausal (51–70 years, n = 12 446), the average age of menopause being taken as 51 years. Young (n = 3022) and older men (n = 19 819) were grouped according to the same age ranges.

Worse clinical stage and histology was more common in premenopausal women than in postmenopausal women, and curative surgery was attempted less frequently (31% *v* 33%, p = 0.03). Lung cancer related deaths were higher in postmenopausal women than in premenopausal women when adjusted for stage, histology, size, grade, and extent of surgery (hazard ratio (HR) 1.14, 95% CI 1.03 to 1.27). Significant covariate adjustment revealed similar lung cancer related deaths in young men and women, but more deaths in older men than in premenopausal women (HR 1.26, 95% CI 1.15 to 1.40). Younger men presented with a more advanced clinical stage than older men, and both male groups had worse presentation and lower crude survival than their female counterparts.

The authors hypothesise that premenopausal NSCLC may be initiated by higher oestrogen concentrations, but any oestrogen exposure in life may confer a protective effect which determines the outcome of the neoplastic process. Age is an important potential confounder in this study. Although survival was higher in women than in men of both age groups, the comparison of the two older age groups was based on crude and not adjusted data. The absence of information about hormone replacement therapy or oral contraceptives is an important omission. Nevertheless, with many of the benefits previously attributed to oestrogen now being called into question, this study should prompt a further more detailed analysis of the effects of oestrogen with respect to lung cancer.

J Ostberg
SpR, University College London Hospitals, London, UK;
j.ostberg@ucl.ac.uk