Pilot study of lung cancer screening for survivors of Hodgkin lymphoma

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Abstract

Hodgkin lymphoma (HL) treatment increases the risk of lung cancer. Most HL survivors are not eligible for lung cancer screening (LCS) programs developed for the general population, and the utility of these programs has not been tested in HL survivors. We ran a LCS pilot in HL survivors to describe screening uptake, participant characteristics, impact of a decision aid and screen findings. HL survivors treated ≥5 years ago with mustine/procarbazine and/or thoracic radiation, were identified from a follow-up database and invited to participate. Participants underwent a low-dose computed tomography (LDCT) reported using protocols validated for the general population. Two hundred and eighteen individuals were invited, 123 were eligible, 102 were screened (58% response rate): 58% female, median age 52 years, median 22 years since HL treatment; 91.4% were deemed to have made an informed decision; participation was not influenced by age, sex, years since treatment or deprivation. Only three of 35 ever-smokers met criteria for LCS through the program aimed at the general population. Baseline LDCT results were: 90 (88.2%) negative, ten (9.8%) indeterminate, two (2.0%) positive. Two 3-month surveillance scans were positive. Of four positive scans, two patients were diagnosed with small-cell lung cancer; one underwent curative surgery. Coronary artery calcification was detected in 36.3%, and clinically significant incidental findings in 2.9%. LDCT protocols validated in ever-smokers can detect asymptomatic early-stage lung cancers in HL survivors. This finding, together with screening uptake and low false positive rates, supports further research to implement LCS for HL survivors (*clinicaltrials gov. Identifier: NCT04986189.*).

Introduction

Two large randomized trials established low-dose computed tomography (LDCT) screening for early detection of asymptomatic lung cancer in the ever-smoking general population. The National Lung Cancer Screening Trial (NLST) which randomized ever smokers aged 55-74 to either a chest radiograph or a LDCT scan of the thorax, reported a 20% reduction in lung cancer mortality in the LDCT arm.[1] The NELSON (Nederlands–Leuvens Longkanker Screenings Onderzoek) trial randomized ever-smokers aged 50-75 to LDCT screening *versus* no screening and reported a reduction in lung cancer mortality of 24% in men and 33% in women.[2] Following the successful roll-out of 'Lung Health Checks' in England[3] incorporating lung cancer screening for those at high risk, in September 2022 the UK National Screening Committee recommended a national lung cancer screening program. People aged 55-74 who are at risk of lung cancer due to smoking are eligible for screening if they meet a prespecified risk threshold determined by one of two lung cancer risk calculators.[4]

Survivors of Hodgkin lymphoma (HL) treated with procarbazine or mustine alkylating agent chemotherapy and/or thoracic radiation[5] are at excess risk of treatment-related lung cancer, with a standardized incidence ratio 6.4 and 30-year cumulative incidence 6.4%.[6] Since most HL survivors lack a significant smoking history, most at-risk survivors do not meet the lung cancer risk threshold for lung cancer screening.[7,8] A targeted lung cancer screening program is, therefore worthy of exploration in this under-represented risk group. Here, we report results of a lung cancer screening pilot in HL survivors using established protocols developed for the general population.

Methods

Patients

Ethical approval for the study was granted by the Wales REC 7 ethics committee (21/WA/0137). Participants were identified from a database of lymphoma survivors held at the Christie NHS Foundation Trust (ADAPT). Eligible individuals had a history of HL (classical HL or nodular lymphocyte-predominant HL [NLPHL]) with no relapse within 5 years (indicating a high likelihood of cure), current age 18-80, treatment with radiation the lung and/or procarbazine or mustine chemotherapy, and registered address within 40 miles of the Christie hospital. The study exclusion criteria are described in the *Online Supplementary Appendix*. The study followed the principles of the Declaration of Helsinki.

Study procedures

Study invitation was by post and non-responders were contacted by telephone after 4 weeks. Interested persons were sent a participant information sheet and a decision aid booklet, entitled 'Screening to find the early signs of lung cancer after treatment for Hodgkin lymphoma: helping you decide'.[10] Participants who provided written informed consent underwent a baseline LDCT scan. The effective radiation dose expected to be below 3 millisieverts (mSv). Pulmonary nodules were reported and managed according to the British Thoracic Society (BTS) Guidelines for the Investigation and Management of Pulmonary Nodules[11] (see *Online Supplementary Appendix* for further information). Participants with negative scans were not offered further screening, whilst participants with indeterminate scans were offered 3-month surveillance LDCT scans. Participants with positive scans were referred to lung cancer services. Coronary artery calcification (CAC) was graded in line with published guidelines.[12] Incidental findings were reported.

Postal questionnaires were sent with the invitation letter (time point 1), with the decision aid (time point 2) and completed at the study visit (time point 3). Lung cancer screening knowledge (measured using a 16-item scale adapted from a questionnaire[13]) and attitude towards lung cancer screening (measured using a 4-item attitude scale based on the work of Marteau *et al.*[14]) were measured at time points 1 and 2. The decisional conflict scale (DCS),[15] preparedness for decision making scale[16] and multidimensional measure of informed choice (MMIC)[14,17] were measured at time point 2. Further details relating to the use of the MMIC can be found in the *Online Supplementary Appendix*. The questionnaire at time point 3 contained questions regarding health, smoking history and respiratory symptoms, including the Medical Research Council (MRC) dyspnoea scale.[18]

Study outcomes

The primary outcomes were the response rate to the initial invitation strategy (letters and telephone calls), and the uptake rate (participants who consented and proceeded with the LDCT scan) among eligible responders. Secondary outcomes included invited cohort demographics, decision making outcomes and scan findings.

Statistical analysis

Uptake rates, scan findings, and results of the DCS and preparation for decision making scale (PDMS) and the measure of informed decision making are reported descriptively. Wilcoxon signed rank test was used to compare matched knowledge scores (which had been converted to the percentage of correct answers) and attitude scores. The characteristics of participants *versus* non-participants were compared using χ^2 test for sex, the independent samples *t* test for age and time since treatment and Mann-Whitney *U* for index of multiple deprivation (IMD) decile and baseline knowledge score and attitude score.

Results

Characteristics of participants and non-participants

Two hundred and eighteen individuals were invited to participate, there were 123 eligible responders and 102 participated. Table 1 shows the characteristics of the invited cohort, participants and non-participants. In summary, among the invited cohort, 54% were female and 46% male, the mean age was 52, and the mean numbers of years since HL treatment was 20. Treatment related risk factors in the invited cohort were: 110 (50.5%) radiation to the lung only; 88 (40.5%) chemotherapy and radiotherapy; 20 (9.0%) chemotherapy only. Among 102 screened participants, 58% were female, the mean age was 52 and the mean number of years since treatment was 22. Treatment-related risk factors in the participants were: radiation to the lung only (N=50, 49%); chemotherapy and radiotherapy (N=43, 42%); chemotherapy only (N=9, 9%); 65.7% were never smokers, 27.5% were former smokers and 6.8% were current smokers. The mean pack years of smoking was 15 (range 0.5-49). Age, sex, index of multiple deprivation decile,[9] time since treatment and baseline lung cancer risk and screening knowledge were not associated with participation. A more positive attitude (measured as a continuous variable) towards lung cancer screening at baseline (measured in 121 people) was associated with screening participation (P<0.01, effect size [r coefficient] 0.2).

Response rate and screening uptake rate

The response rate to the invitation (including letter and phone call for initial non-responders) was 58.3% (127/218). A reminder phone call was made to 73 people who did not respond to the initial invitation and 27 (37%) of them subsequently participated. The screening uptake rate among

eligible responders was 82.9% (102/123). Response rate, uptake rate and scan outcomes for participants are shown in Figure 1.

Decision making outcomes

Matched data on lung cancer screening related knowledge and attitude towards lung cancer screening were available for 95 individuals. Exposure to the decision aid improved lung cancer screening related knowledge ($P<0.001$) but did not affect attitude towards lung cancer screening ($P=0.44$) as shown in Table 2. The proportion responding correctly to each individual item in the knowledge scale pre- and post-exposure to the decision aid is shown in *Online Supplementary Table S1* in the *Online Supplementary Appendix*. DCS scores and PDMS scale score were calculable for 97 and 96 individuals respectively, as shown in Table 3. Out of a possible total of 100, the median total DCS score was 9, the median uncertainty score was 8, and the median score was 0 for the effective decision, informed, values clarity and support subscales. The median score on the PDMS scale was 80 out of 100. 91.4% were deemed to have made an informed decision.

Participants' health and respiratory symptoms

Fourteen participants (14%) had been diagnosed with another primary cancer following HL (6 carcinomas of the breast, 1 ductal carcinoma *in situ*, 1 thyroid, 4 skin [2 basal cell carcinomas, 1 melanoma and 1 not specified], 1 prostate, 1 cervical).

We examined respiratory symptoms in the cohort. Breathlessness, as measured by the MRC Dyspnoea Scale, was reported only with strenuous exertion by 59% (grade 1) or with hurrying by 37% (grade 2); 3% walked slower than contemporaries (grade 3) and 1% stopped after walking 100 m (grade 4) due to breathlessness. Other reported symptoms included a cough most days/nights (14%), the regular production of phlegm (24%) and wheezing in 20%. Over the previous 12 months, 8% had received antibiotics or steroids and 1% had been admitted to hospital to treat a respiratory illness.

Selecting from a list of 20 conditions, 38% reported no comorbidities, 54% selected 1-2 comorbidities and 8% reported three or more comorbidities. The frequently recorded comorbidities were asthma (21%) and hypercholesterolaemia (21%).

Table 1. Characteristics of the overall invited sample, participants and non-participants.

	Overall invited cohort N=218	Participants N=102	Non-participants N=106	*P*
Sex: Male /Female, N (%)	101/117 (46/54)	43/59 (42/58)	51/55 (48/52)	0.47
Mean age in years (range)	52 (25-80)	52 (26-80)	51 (29-80)	0.52
Mean IMD decile (range)	6 (1-10)	6 (1-10)	6 (1-10)	0.14
Mean number of years since last treatment (range)	20 (6-45)	22 (7-44)	20 (6-45)	0.08
Diagnosis, N (%)	Classical HL: 206 (94.5) NLPHL: 12 (5.5)	Classical HL: 98 (96) NLPHL: 4 (4)	-	-
Treatment-related risk factor: chemotherapy only, N (%)	20 (9)	9 (9)	-	-
Treatment-related risk factor: radiotherapy to lung only, N (%)	110 (50.5)	50 (49)	-	-
Treatment-related risk factor: chemotherapy and radiotherapy to lung, N (%)	88 (40.5)	43 (42)	-	-
Ethnicity, N (%)	-	White British 93 (91.2), Asian (2) Black African (1), Black British (1) Irish (2), White and black Caribbean (1) White and Asian (1), not divulged (1)	-	-
Smoking status %	-	Never smoker 65.7, former smoker 27.5, current smoker 6.8	-	-
Comorbidities, N (%)	-	None (38.2), 1-2 (54), ≥3 (7.8)	-	-
Educational attainment %	-	No qualifications (9.8), school/ college/ further education but not a degree (52.9), undergraduate degree (21.6), postgraduate degree (15.7)	-	-

IMD: index of multiple deprivation; HL: Hodgkin lymphoma; NLPHL: nodular lymphocyte-predominant HL.

Participants' eligibility for lung cancer screening programmes aimed at ever smokers in the general population

Six-year lung cancer risk was calculated using an online $PLCO_{m2012}$ calculator[20] for 29 participants who were current and former smokers and aged 40 or over (representing the scope of the calculator rather than the age-range eligible for lung cancer screening). Data were missing for the additional six ever-smokers. The median risk was 0.3% (range, 0.1-12.2%) and only three (2.9% of all participants) met the eligibility criteria for lung cancer screening aimed at ever-smokers in the UK (a current age of 55-74 and a 6-year lung cancer risk of ≥1.51%).[21]

Low-dose computed tomography scan outcomes

The results of LDCT scans are shown in Figure 1 and are also described here. Regarding baseline scans: 90 (88.2%) were negative, ten (9.8%) indeterminate, two (2.0%) positive. Nine of ten participants with an indeterminate baseline scan underwent 3-month surveillance scans. Of these, two had positive surveillance scans, and the rest had stable nodules (6/7) or resolved nodules (1/7). One participant with an indeterminate scan result fulfilled the BTS guidelines criteria for a 12-month surveillance scan without a 3-month scan.

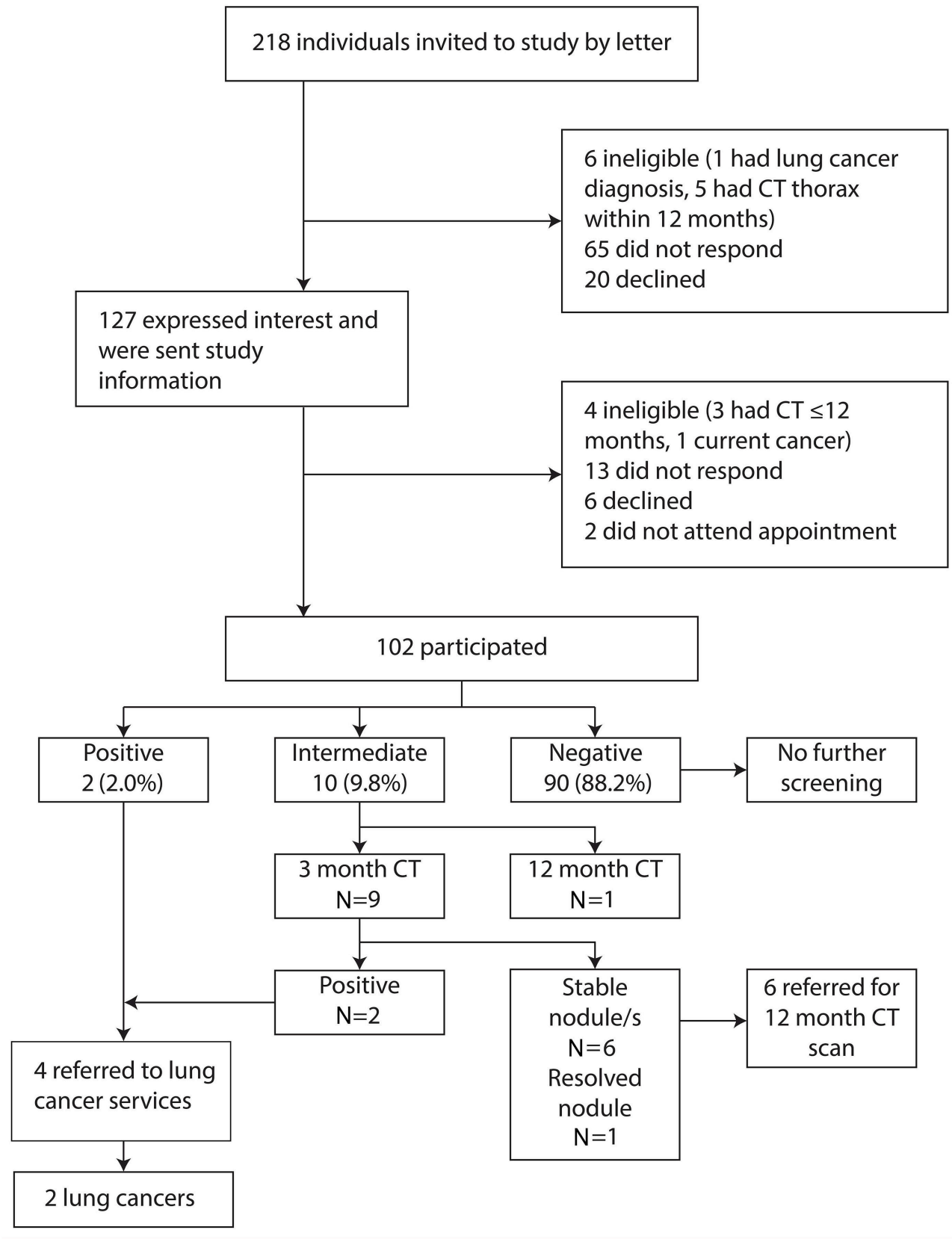

Figure 1. Lung cancer screening participation rates and scan outcomes. CT: computed tomography.

Table 2. Knowledge of and attitude towards lung cancer screening before and after exposure to the decision aid.

Knowledge and attitude scores N=95			
	Pre-exposure to decision aid	**Post-exposure to decision aid**	***P* for difference pre and post**
Median percentage of correct responses on knowledge scale	56	88	<0.001
Mean attitude score	19	19	0.44
Median attitude score	21	21	-
Range (IQR)	3-21 (2)	10-21 (3)	-

IQR: interquartile range.

The outcomes of the four participants with a positive LDCT scan are detailed in Table 4. Two patients have been diagnosed with small-cell lung cancer, one of whom underwent surgical resection. Notably, neither of them met the risk threshold for lung cancer screening for ever smokers. Neither of the remaining two participants with a positive LDCT scan have been diagnosed with lung cancer, giving a false positive rate of 50% of cancer service referrals (N=2/4), or 2% (N=2/102) of all those screened. There were no complications from invasive procedures.

CAC was detected on baseline LDCT in 36.3% of participants (severe in 4.9%, moderate in 6.9% and mild in 24.5%), of whom 43.2% reported a history of angina/myocardial infarction/hypertension, and the remainder reported none of these conditions. If coronary artery calcification was detected, the participants' general practitioner was informed by letter, and blood pressure and cholesterol level checks were proposed. Aortic valve calcification was present in 5.9% and mitral valve calcification in 1.9%.

Incidental findings were reported in 64.7% of baseline scans. The clinical significance of each incidental finding was determined by an investigator (detailed in Table 5). Only 2.9% were of immediate clinical significance.

Table 3. Decisional conflict scale and Peabody developmental motor scale scores following exposure to the decision aid.

DCS scores N=97 Higher scores indicate higher decisional conflict	
	Median (range; IQR)
Total DCS score (0-100)	9 (0-42; 25)
Uncertainty subscale score (0-100)	8 (0-67; 25)
Effective decision subscale score (0-100)	0 (0-50; 25)
Informed subscale score (0-100)	0 (0-50; 25)
Values clarity subscale score (0-100)	0 (0-67; 25)
Support subscale score (0-100)	0 (0-50; 25)
PDMS scores N=96 Higher scores indicate greater preparedness for decision making	
Total score (0-100)	80 (35-100; 8.5)

DCS: decisional conflict scale; PDMS: preparation for decision making scale; IQR: interquartile range.

Discussion

We report the largest lung cancer screening study performed in HL survivors to date. The rate of response to the initial invitation was 58.3% and the uptake rate among eligible responders was 82.9%. The prevalence of lung cancer after a single round of screening in this study was 2.0%. This study found that the novel decision aid improved lung cancer risk and screening related knowledge and was associated with low levels of decisional conflict and high preparedness to make a decision about screening - key requirements for patient decision aid tools.[22] This supports its' use in future lung cancer screening studies in this population. In addition, a large majority of those who received the decision aid booklet made an informed decision according to the MMIC. However, there is no consensus as to how to define 'good' knowledge or a 'positive' attitude, both requirements of the MMIC, leading to variation in the way these measures are defined in practice.[23] We have reported individual item results from knowledge scales (in *Online Supplementary Appendix*), tested associations between aspects of informed decision making (e.g., knowledge/attitude and participation), and used other measures (DCS, PDMS) to enhance our reporting of informed decision making.[24]

In relation to the response rate and uptake rate among eligible responders, there were no predefined thresholds for success. However, our response rate was similar to the response rates of high-risk ever smokers in the London-based Lung Screen Uptake Study[10] (53%) and the Yorkshire Lung Screening Trial[19] (50%). Furthermore, our screening uptake rate was comparable to the Yorkshire Lung Screening Trial (screening uptake rate 86.8%).[19] A number of strategies could be employed to improve on our response rate. The decision aid was not provided upon first contact to avoid

provoking anxiety among those who would not wish to participate. Providing the decision aid upfront - reflecting the approach used by established cancer screening programs[25,26] - might increase the response rate by providing more information on first contact, although this is speculative and could be tested in a randomized study. Client reminders, small media, one-on-one education and reducing structural barriers have been shown in a systematic review to be potential strategies for increasing uptake of cancer screening programs, although the strength of evidence varies across different cancer screening programs.[27] Larger studies of lung cancer screening studies for HL survivors will be a valuable opportunity to test the impact of one or more of these measures on uptake, potentially through a randomized trial comparing differing invitation and communication strategies.

The benefit of lung cancer screening in the high-risk ever-smoking population is well described, specifically that detection of asymptomatic early-stage lung cancers increases rates of surgical resection and treatment with curative intent, leading to improved lung cancer specific survival.[1] However lung cancer screening has risks, including those arising from radiation and from a false-positive result and the anxiety associated with an indeterminate nodule-requiring surveillance. Compared to a standard CT scan which delivers an average dose of 7 mSv, a LDCT scan

Table 4. Clinical outcomes in participants with a positive low-dose computed tomography scan.

Case	Timing and nature of positive scan	Personal demographics and diagnosis	Treatment and smoking history	Further investigations	Lung cancer diagnosis and treatment
1	Baseline scan	Female, age range 50-60, classical HL	Procarbazine, never smoker	3 surveillance CT scans at 3-month intervals, and a PET/CT scan	None
2	Baseline scan	Male, age bracket 60-70, classical HL	Procarbazine, radiation to lung, never smoker	Pleural aspiration, 2 surveillance CT scans	None
3	3-month surveillance LDCT scan	Male, age bracket 60-70, classical HL	Procarbazine and radiation to lung, ex-smoker (30 pack years)	PET/CT scan, MRI brain	Small cell lung cancer stage T2N0M0; wedge resection followed by adjuvant chemotherapy (curative intent)
4	3-month surveillance LDCT scan	Male, age bracket 50-60, classical HL	Procarbazine, radiation to lung, smoker (20 pack years)	PET/CT scan	Stage 3 small cell lung cancer, referred for palliative chemotherapy

HL: Hodgkin lymphoma; CT: computed tomography; PET: positron-emssion tomography; MRI: magnetic resonance imaging; LDCT: low-dose CT.

Table 5. Incidental findings on low-dose computed tomography scans: significance, nature and number affected.

Category, N affected (% of total cohort)	Nature of finding (N of participants affected)
Clinically significant, 3 (2.9)	Distended left pelvi-calyceal system (1) Pleural effusion (in a participant with a positive baseline scan in whom lung cancer is now considered unlikely) (1) Vertebral bone metastases (breast cancer recurrence) (1)
Potentially clinically significant, 15 (14.7)	Emphysema (4) Cardiomegaly (2) Inflammation in the lungs (3) Bronchiectasis (2) Fatty liver infiltration (1) Vertebral wedge collapse / end plate fractures (2) Hiatus hernia (1)
Not clinically significant, 48 (47.1)	Post-radiotherapy fibrosis / scarring (21) Residual nodes / mass at site of previous disease (usually calcified) (27) Vertebral body sclerosis (1) Adrenal myelolipoma (1) Congenital vertebral fusion (1) Subpleural atelectasis (1) Liver cyst (2) Apical pleural thickening (1)

delivers an average of 1.4-1.6 mSv.[28] The risk of developing a malignancy due to radiation from one or more LDCT scans is, therefore minimized. An analysis on five UK-based lung cancer screening programs found an overall false-positive rate of 2%, the rate of invasive tests for attendees without lung cancer 0.6% and 11.1% of scans were indeterminate.[3] In this study, the false-positive rate was also 2% and one participant (1% of participants) underwent an invasive investigation (a pleural aspiration), without a subsequent diagnosis of lung cancer. The rate of detection of indeterminate nodule/s in this study was 10%. Our rates of false-positive results, invasive tests in those without lung cancer and indeterminate nodules are similar to those in high-risk ever smokers screened for lung cancer. The impact of undergoing lung cancer screening on health-related anxiety and quality of life is being further investigated in this study through follow-up questionnaires administered at 2, 6- and 12-months following screening; data collection is ongoing.

In terms of incidental findings on LDCT, reassuringly only 3% required an immediate intervention. CAC was detected in around a third of our participants, compared with 61.9% in the Lung Screen Uptake Study,[29] probably because our participants were younger and largely never smokers. The presence of CAC was predictive of death related to coronary artery disease in NLST;[30] 11.8% of our participants had moderate or severe CAC. Given that cardiac events are the second most common cause of death in HL survivors,[31] CAC detection through lung cancer screening could be an opportunity to initiate primary prevention which would be of particular importance for individuals without a history of cardiovascular disease.

Implementing lung cancer screening programs for high-risk ever-smokers has been deemed to have a health economic benefit.[32–34] The only published cost-effectiveness analysis of lung cancer screening for HL survivors was performed in 2014 in the United States. The study suggested that screening may only be cost effective for smokers.[35] A country-specific updated analysis would be required to understand the economic impact of lung cancer screening for this group in the contemporary era.

A limitation of this study was the lack of data on smoking history and ethnicity for non-participants, meaning we cannot comment on the impact of ethnicity, or whether smokers were less likely to participate, as has been the case with other lung cancer screening trials.[36,37] Some of those invited to this study had been invited to and/or participated in other late effects research studies, including studies exploring HL survivors' willingness to be screened for lung cancer which also recruited using the ADAPT database.[8,38] Those who had previously been contacted about these studies may have had increased awareness about lung cancer risk and screening, increasing their motivation to participate. Therefore, uptake of lung cancer screening by the cohort invited to our study may not be representative of the uptake by HL survivors who lack prior awareness of lung cancer risk and screening.

The results of this pilot support the development of a larger study of lung cancer screening for HL survivors. The main challenge facing the development of a larger study will be identifying HL survivors at a high risk of lung cancer. Older age at the time of HL treatment and increasing years of follow-up since treatment are both risk factors for lung cancer.[39] These factors would be identifiable from the National Cancer Registry and Analysis Service (NCRAS) database. However, to fully capture lung cancer risk, it will be necessary to collect data on chemotherapy and radiotherapy treatment received, since alkylating agents and thoracic radiation are important risk factors for lung cancer in this group. In addition, HL survivors treated in the modern era are expected to be at significantly lower risk than those treated decades ago with higher doses of radiotherapy and alkylating agents and may benefit less from lung cancer screening. The NCRAS database holds personal data for HL patients diagnosed over several decades but does not contain treatment data with the required granularity to determine those at excess risk of lung cancer. This information may need to be sought from treating centers, which would take significant time and effort. This approach was used in the creation of the Breast Cancer After Radiotherapy Dataset (BARD),[40] which has identified around 8,000 women treated with radiotherapy under the age of 30 and at risk of breast cancer; we may learn from the successes of this project. The optimal frequency of lung cancer screening in high-risk ever-smokers in the general population has not yet been established and work is ongoing.[4] The frequency of screening for HL survivors would ideally be determined by a personalized lung cancer risk assessment, taking into account the relevant risk factors.

Disclosures

No conflicts of interest to disclose.

Contributions

RB designed the protocol, recruited patients, collected and analyzed data and wrote the manuscript. KL, PC, CA and JR advised and contributed to the protocol development and data analysis and supervised the study. BT, ST and JM contributed to protocol development and reported low-dose CT scans. All authors approved the final manuscript.

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Data-sharing statement

The study protocol can be obtained by contacting the corresponding author. The study data will not be made available.

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