Probability of cancer in lung nodules using sequential volumetric screening up to 12 months: UKLS trial.

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Abstract

Background Estimation of the clinical probability of malignancy in patients with pulmonary nodules will facilitate early diagnosis, determine optimum patient management strategies and reduce overall costs.

Method Data from the UK Lung Cancer Screening (UKLS) trial were analysed. Multivariable logistic regression models were utilised to identify independent predictors and to develop a parsimonious model to estimate the probability of lung cancer in lung nodules detected at baseline, three month and twelve month repeat screening.

Results Of 1994 participants that underwent CT scan, 1013 participants had a total of 5063 lung nodules and 52 (2.6%) of the participants developed lung cancer during a median follow-up of 4 years. Covariates that predict lung cancer in our model included female gender, asthma, bronchitis, asbestos exposure, history of previous cancer, early and late onset of family history of lung cancer, smoking duration, forced vital capacity, nodule type (pure ground glass and part solid) and volume as measured by semi-automated volumetry. The final model incorporating all predictors had excellent discrimination; area under the receiver-operating characteristic curve (AUC [95% CI] = 0.885 [0.880 to 0.889]). Internal validation suggested that the model will discriminate well when applied to new data (optimism-corrected AUC = 0.882 [0.848-.907]). The risk model had a good calibration (goodness-of-fit $\chi(8)$ 8.13, P = 0.42).

Conclusions Our model may be utilised in estimating the probability of lung cancer in nodules detected at baseline, and three months and twelve months from baseline, allowing more efficient stratification of follow-up in population-based lung cancer screening programs.

Key Messages

- What is the key question?

To develop a lung cancer pulmonary nodule risk model which incorporates volumetric measurements.

- What is the bottom line?

The UKLS pulmonary risk model has excellent discrimination; area under the receiver-operating characteristic curve (AUC [95% CI] = 0.885 [0.880 to 0.889] and has good calibration (goodness-of-fit $\chi(8)$ 8.13, P = 0.42).

- Why read on?

The potential for the UKLS Nodule Risk Model (UKLS-NRM) is that it may be utilised in future national CT screening programmes, which incorporates volumetric measurements to identify malignant pulmonary nodules.

Introduction

Lung cancer is the most common cause of cancer death in Europe and has the highest economic cost (€18·8 billion, 15% of overall cancer costs).[1] All respiratory illness in the UK costed £11·1 billion in 2014.[2] Despite recent improvements, thought to be related to improved resection rates, 5-year survival for all stages is only 13%, but >80% for patients with stage 1a disease. [3-5] The poor survival outcome is partly attributable to variation in resection rates but mainly due to late presentation of the disease when surgical resection or other treatment options are less effective.[6]

Low Dose Computed Tomography (LDCT) is a viable screening tool for early lung cancer detection and mortality reduction. The USA-based National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality relative to chest x-ray screening.[7] Results of the on-going Dutch-Belgian NELSON trial and pooled European randomised controlled trials are awaited.[8] In the NLST and other (smaller) trials, over 20% of LDCT-screened participants had indeterminate lung nodules (i.e. potentially cancerous, but of insufficient size to refer for treatment), and thus required further CT scans. Diagnostic stratification of indeterminate pulmonary nodules is currently based on radiological characterisation including nodule diameter and/or volume and risk prediction models. Indeed two risk prediction models, used sequentially are recommended in the latest British Thoracic Society (BTS) guidelines[9], the Brock University model, for nodules ≥300mm^3 or ≥8mm diameter,[10] and where the risk is estimated at >10%, the Herder model after PET-CT.[11]

However, none of these models employ volumetry and all are for use at baseline. Nodule volumetry provides a more accurate assessment for baseline size and subsequent growth than diameter measurements.[12] Nodule volume is the preferred method for evaluation in the BTS guidelines and recommended as a more accurate method in the latest Fleischner

Society guideline.[13] It appears in several diagnostic algorithms but is insufficient in isolation.[14,15] It is therefore crucial to improve strategies to quantify the risk of malignancy in 'indeterminate nodules'. This allows participants in screening programmes to be simply returned to the next planned screen and patients to be reliably advised about the need for follow-up or referral for clinical work-up.

There is a growing recognition of the potential utility of risk models to predict lung cancer risk in patients with pulmonary nodules, thus allowing more subjects to be monitored with low dose imaging rather than needing minimally invasive or invasive procedures.[16,17] The characteristics of pulmonary nodules detected on screening CT scans may determine optimum patient management strategies because risk-based selection of patients have been reported to precisely delineate the benefits and harms of screening by accommodating detailed information on lung cancer risk factors.[18] The aim of this study was to develop a model to predict the risk of lung cancer in screen detected pulmonary nodules detected at baseline, 3 month or 12 month interval CT screening.

Methods

Study design and participants

The United Kingdom Lung Cancer Screening (UKLS) Trial is a multicentre randomised controlled pilot trial of LDCT screening versus standard care for the early detection of lung cancer in high-risk individuals.[15,19,20] The UKLS was approved by the National Information Governance Board and ethical approval was given by the Liverpool Central Research Ethics Committee in 2010 (reference number 10/H1005/74). The trial was registered with the International Standard Randomised Controlled Trial Register under the reference 78513845.

Primary care trust (PCT) records were used to approach 247,354 individuals aged 50–75 years, residing in specific health care areas (Liverpool, Knowsley, Sefton, Cambridgeshire,

Peterborough and Bedfordshire) by letter to participate in the trial. The Liverpool Lung Project lung cancer risk prediction model (LLP_{v2}) was utilised to calculate risk scores to identify those at high risk (≥5% over 5 years) of developing lung cancer.[21] A total of 4055 high-risk individuals were recruited and randomised, 2028 into the CT arm (of whom 1994 underwent a CT) and 2027 received usual care. At the time of reporting the UKLS identified 1.7% lung cancers at baseline which was significantly higher than either the NELSON or NLST baseline data. This study presents the result of 1013 of the 1994 participants with at least one non-calcified lung nodule at baseline, 3 month and 12 month repeat LDCT.

Thoracic CT scans

Details of the CT scans have been described previously.[20] Briefly, thoracic CT images were obtained from lung apices to bases, during suspended inspiration, in a single breath hold and without the administration of intravenous contrast. Images were reconstructed at 1 mm thickness at 0.7 mm increments, using a moderate spatial frequency kernel reconstruction algorithm. Acquisition parameters (kVp and mAs) varied according to body habitus to achieve a CT dose index below 4 milliGray.

Reading methods

All CT scans were read using the 'LungCARE' (LungCARE, version Somaris/5 VB 10A, Siemens Medical Solutions) on the Syngo Siemens workstation, which provides a value for nodule size based on volume. To optimise sensitivity and specificity, all baseline CT scans were read by two thoracic radiologists at both local (Liverpool Heart and Chest Hospital or Papworth Hospital) and central (Royal Brompton Hospital) sites.[15] All discrepancies were resolved by a review from the third thoracic radiologist at the Royal Brompton site and after

reaching a consensus, a letter outlining the results of the scan is sent to the participant and their GP.[15]

Nodules: classification and management

The management of pulmonary nodules within the UKLS trial has been reported in detail in the full HTA report. [20] Four categories of nodules were reported (Figure 1, provides the full details for solid, part solid and pure ground glass nodules): Category1 (benign nodule <3mm, diam. 15mm^3) ; Category 2 (Vol. 15- 49mm^3 3-4.9mm); Category 3 (Vol. 50-500mm^3, 5-9.9mm); Category 4 (Vol. >500mm^3 or >10mm). All Category 2, 3 and 4 nodules were included in this analysis. The number of nodules identified in each of the three Categories are shown in Table 2.

All of the nodules identified in the baseline scan were re-analysed in the follow up CT scans at 3 and 12 months, except the malignant ones which had been resected. Thus, all of the UKLS reported nodules at 3 or 12 months were originally matched with the baseline scan. Stable baseline nodules were only counted once, i.e. at baseline, however, if a nodule developed new characteristics at 3 or 12 months, they were excluded from the analysis. Significant growth of nodules was defined based on their percentage change in volume and volume doubling time (VDT); i.e. 25% increase in volume and VDT <400 days.

Readers identified up to a maximum of 20 non-calcified nodules per subject. Nodules were categorized as solid, part-solid or pure ground-glass (pGGN) and further classified into four categories based on size reflecting their probability of being malignant as depicted in Table

1.[15] Solid nodule outline was also recorded as, smooth, polylobulated, spiculated or irregular. Smooth was defined as a continuous regular outline. Lobulation was defined as areas of bulging of the lesion contour. Spiculation was defined as the presence of strands extending from the lung margin into the lung parenchyma. Irregular was defined as not smooth, polylobulated or spiculated. pGGN are defined as a nodule composed of a focal area of hazy increased lung opacity that does not obscure the underlying structures.[9] Whenever follow-up scans (at 3 or 12 months) were performed, the volume doubling time (VDT) of the solid nodule was calculated, in the cases where nodule segmentation was reliable at baseline and follow-up. In the UKLS, we used manual diameter for i) ground glass and part solid nodules, ii) subpleural nodules and iii) nodules where volumetry was recorded as being unreliable, these nodules were excluded from the analysis.

The diagnosis of lung cancer was made by histopathological examination of the resected specimen, otherwise it was based on the radiological clinical diagnosis. Quality control of the specimen involved exchange of a representative haematoxylin and eosin-stained section from all cases between reference thoracic pathologists at Liverpool and Papworth. This was accompanied where necessary by any immunolabelled sections used in diagnosis and or classification of lesion. Sections were blinded reviewed and responses were exchanged with appropriate discussion in case of discordance.

Statistical analyses

Descriptive statistics were obtained and compared by using the χ^2 test or the Fisher's exact test for categorical variables. Complete case analysis i.e. omitting covariates with missing data in regression models could lead to bias.[22] Therefore, multiple imputation (MI) of missing data by chain equations was performed to impute missing data across multiple covariates simultaneously. The MI process was implemented in three steps: (1) imputation step, (2)

analysis step and (3) pooling step. The results of the analyses were pooled by applying the Rubin's rules.[23] Graham et al., using simulations recommended the use of many more imputations than the classical recommendation of three to five imputations so we used 20 imputations based on their recommendation.[24] The results of the analyses with imputation of missing covariates were similar to that of complete case analyses (Supplementary Information Table S1). Multivariable logistic regression models were constructed to estimate the probability that lung nodules detected at baseline, 3 month or 12 month LDCT screening were malignant. Variable selection was informed by the known and potential risk factors for lung cancer in the literature, clinical importance, confounding, collinearity, model stability and statistical significance. Variables considered for inclusion included age, gender, BMI, history of respiratory diseases (asthma, bronchitis, emphysema, pneumonia, tuberculosis and COPD), exposure to asbestos, previous history of cancer excluding lung cancer, family history of lung cancer, previous CT scan, previous X-ray, forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). In addition, we also considered available nodular characteristics including nodular volume, nodule location, nodule type and nodule count (intrapulmonary lymph nodes were not included). Volume doubling time was assessed but insufficient data available for the UKLS risk model analysis. The multivariable model was built in two phases. First, all covariates with $P \leq 0.10$ in the univariate analyses were considered for inclusion in the multivariable model. Second, a backward selection procedure with ($P < 0.05$) was used to choose the covariates in the final multivariable model.[25] Covariates eliminated were re-entered in the final multivariable model, with adjustment for the remaining significant covariates to ensure that no omitted covariate significantly reduced the log likelihood χ^2 of the model.[25] The unit of analysis was undertaken on a per nodule basis and since some individuals had multiple nodules, the variances of effect estimates were adjusted for data clustering within individuals using the Huber-White robust (sandwich) variance estimator. [26]

Nonlinear effects of continuous variables were evaluated using fractional polynomials.[27] The performance of the multivariable model was quantified by assessing its discrimination and calibration. Discrimination (ability to classify correctly) was assessed using the area under the receiver-operating characteristics curve (AUC). Model calibration was evaluated using Hosmer-Lemeshow goodness of fit test, and the Deviance and Residual test.[28] The overall model performance was evaluated using the Brier score.[29] Bootstrapping techniques were used for internal validation of the model and bootstrap samples were drawn 200 times with replacement.[30] Regression models were created in each bootstrap sample and tested on the original sample to obtain stable estimates of the optimism of the model, i.e., how much the model performance was expected to decrease when applied in new datasets.[31-33] All analyses were performed using Stata®14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP) and SAS®9.4 (SAS Institute Inc, Cary, NC).

Results

Of 1994 participants that underwent CT scan, 1013 participants had a total of 5063 lung nodules and included the 52 (2.6%) of the participants developed lung cancer during a median follow-up of 4 years. There were 979 Category 1 Patients who had no nodules reported as per UKLS Protocol. The mean age of the 1013 participants is 67.8±4.1 years. There was no significant difference between the age of participants with benign and malignant nodules. In subjects with malignant nodules, a greater proportion were female that in those with benign nodules" (32.7% vs 26.4%). Participants with malignant nodules had a longer smoking duration than participants with benign nodules (44.4±7.7 vs 41.3±10.3) years. COPD was more common in participants with malignant nodules compared to those with benign nodules (17.3% vs 2.5%). Patients with a malignant diagnosis had larger nodules than patients with benign nodules

(P <0.0001). Furthermore, there were significant differences between FEV1, FVC, volume, nodule counts and nodule types between benign and malignant nodules (Table 3).

In univariate analysis, female gender (OR, 2.407; 95%CI, 1.819-3.185), smoking duration (OR, 2.407; 95%CI, 1.819-3.185), pneumonia (OR, 1.444; 95%CI, 1.093-1.908), asthma (OR, 1.764; 95%CI, 1.326-2.346), tuberculosis (OR, 2.026; 95%CI, 1.514-2.710), COPD (OR, 2.062; 95%CI, 1.549-2.744), family history of lung cancer, early onset (OR, 3.694; 95%CI, 2.696-5.026); late onset (OR, 2.062; 95%CI, 1.508-2.820), BMI (OR, 0.963; 95%CI, 0.933-0.994), FEV1 (OR, 0.289; 95%CI, 0.233-0.359), FVC (OR, 0.313; 95%CI, 0.262-0.375), nodular volume (OR, 1.001; 95%CI, 1.001-1.001) and nodule counts (OR, 0.977; 95%CI, 0.958-0.996), pGGN type (OR, 3.106; 95%CI, 1.674-5.764) were significantly associated with malignancy in a nodule.

Table 4 presents the final multivariate logistic regression model. Age, female gender, asthma, bronchitis, exposure to asbestos, previous malignancy, family history of lung cancer (early and late onset), smoking duration, forced vital capacity nodule type (pGGN and PSN), nodule location (upper vs middle or lower lobe) and nodular volume were included in the model. The model had very good discrimination with an AUC of 0.885(95% CI, 0.880–0.889; Figure 2) and 0.882 (95% CI, 0.848–0.907) by internal validation with bootstrap resampling and correction for optimism. The Hosmer–Lemeshow goodness-of-fit test demonstrated an excellent calibration $\chi^2(8)$ 8.13, P = 0.42. Likewise, the Deviance *(P* = 1.00) and Pearson goodness of fit (P = 0.223) statistics indicates that the fitted model is appropriate. The overall model performance evaluated using the Brier score gives a P -value = 0.034.

Discussion

The clinical management of pulmonary nodules is challenging because of the need to distinguish benign and potentially malignant nodules. These challenges will become more

widespread if LDCT national screening is introduced. In this study, we utilised data from the UKLS pilot trial to develop and internally validate a risk model for estimating the probability of lung cancer in pulmonary nodules detected utilising the baseline, three month and twelve-month data, from baseline. Our model had very good discrimination, excellent calibration and overall model performance. and internally validated using bootstrapping.

An increasing number of malignancy risk prediction models have been proposed for categorising indeterminate pulmonary nodules. Some of these models may be subject to biases due to small sample size and retrospective study design.[34,35] However, some models have been evaluated and compared in external case series and some show good discrimination.[36-38] The two models with the highest accuracy were recommended for use in the BTS guidelines.[9-11]

Although our model gave values for discrimination and calibration comparable to the two models recommended in the BTS guidelines, we cannot directly compare it with these models because accuracy can vary considerably, within populations. However, our model can be easily incorporated into screening protocols because it included readily available, strong, and plausible covariates that have been implicated in the aetiology of lung cancer from our own and numerous other case–control and cohort studies. The model reported in this paper is novel, as it incorporates screen detected nodule volume in the risk prediction calculation. Nodule volume is considered to be more accurate and reproducible than diameter measurements,[39] but its role in lung risk prediction models from clinical trial data has not been previously been used. A previous effort has been made to develop pulmonary risk model incorporating volume in a small cohort from one center, of 221 patents with a 37% malignancy. The co-authors provided three promising models, which correctly classified the predicted malignancy in 83-88% of subjects.[40]

It can be hypothesized that nodule volume is superior to diameter at predicting malignancy because it is a parameter that reflects the size of the entire nodule.

Previous lung diseases such as asthma and bronchitis have been reported as risk factors for lung cancer.[41-43] In our study, asthma and bronchitis were independent predictors of lung cancer in our final multivariable model. The reasoning why bronchitis was found to be significant but neither COPD or emphysema were significant may be explained by misclassification either when there is no disease or asthma is wrongly labelled as COPD. We are unable to confirm this from our data. A second reason is that our smoking data was relatively accurate, and there is some debate about whether COPD is a significant independent risk factor for lung cancer or merely a marker of smoking.[43] However, the protective association of asthma with nodule malignancy observed in our study suggests our source data were at least detecting true asthma, as asthma is not thought to be an independent risk factor for cancer. In a recent meta-analysis, asthma was associated with increased risk of lung cancer but misclassification may have been operative here.[42] In contrast, our observation about bronchitis as an independent predictor of malignancy is in agreement with earlier studies in the literature.[41]

Other risk factors for lung cancer earlier described in the literature such as occupational exposure to asbestos, previous malignancy, family history of lung cancer, smoking duration and FVC were also significantly associated with lung cancer in this study.[21,44] Our observation that female gender is significantly associated with lung cancer is in agreement with the study by McWilliams *et al*.[10] and also in the UK population[43] Our observation that FVC is significantly inversely associated with lung cancer is supported by a recent study by Enomoto *et al*. In their study, they reported that low FVC predicts cytotoxic chemotherapy-associated acute exacerbation of interstitial lung disease in patients with lung cancer.[44] In addition, nodular characteristics such as PGGN type and nodular volume were independent predictors of lung cancer.

Strengths of our study include its study design i.e. a randomised trial, the large number of nodules relative to the participants, a UK socioeconomic representative population, the use of volumetry and detailed information on the main risk factors (such as smoking and family history of lung cancer) was ascertained by closely supervised trained interviewers, using standardized questionnaires.[20]

Limitations of this study are that we did not include spiculation in our model because of the low number of nodules with this feature reported by UKLS radiologists and we were unable to examine the effect of volume doubling time. A second limitation is that the model was developed from a cohort at a particularly high risk of lung cancer, which means there is a possibility that it will perform less well in populations at lower risk. Although the model was developed and internally validated using bootstrapping, a well-established method for internal validation that has been found to be superior to other internal validation techniques,[30] the ultimate test will be validation in an independent population.[33] In addition, the marked geographical variation in incidence rates of lung cancer warrants the evaluation of our model in geographically diverse populations. Another limitation is that we did not evaluate diameter in the model. However, while automated diameter measurements are available from volumetry applications, these measurements are not typically used in screening when reliable volume measurements are available.

Advancement in high-throughput methodologies and routine digitisation of medical records and their application in molecular and genetic epidemiological studies have expanded the potential for "omic"-based risk prediction.[45] In this era of big data, advance statistical techniques, machine learning and deep learning methodologies will continue to emerge so we therefore recommend future studies to explore the utilisation of these methodologies to

integrate omics, imaging, genetics with clinical and other phenotypic characteristics in order to produce robust predictive models that may expedite lung cancer in benign nodules.

In conclusion, we have developed and internally validated a risk model for estimating the probability of lung cancer in nodules detected at baseline, three months and twelve months from baseline. The model is based on readily available, strong, and plausible covariates that have been implicated in the aetiology of lung cancer. The application of the UKLS Nodule Risk Model (UKLS-NRM) has the potential to be used in both the research and clinical setting, in CT screening studies utilising volumetric analysis. The application of our model in identifying nodules at high risk of developing lung cancer in population-based screening programs needs further study.

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Data sharing statement: We are committed in principle to data sharing with fellow researchers and are currently drawing up operating procedures for such. We anticipate that the data will be stored securely in Liverpool and that reasonable requests for data for further research will be accommodated, subject to compliance with regulations, maintaining the integrity of information governance and ensuring no loss of confidentiality on the part of the participants of the study. For requests which require considerable data manipulation and management on our part, this will need to be resourced by those requesting data.

Authors contribution:

Michael Marcus & John K. Field developed the concept and design of the Probability of lung cancer in pulmonary nodules detected at baseline and associated repeat scans, in the UKLS trial utilising nodule volumetry. Anand Devaraj provided expert advice on the radiological interpretation of the UKLS CT images. All of the authors contributed equally to developing and reviewing the manuscript.

Table 1 Nodule: categories, morphology and management

Categories	**Solid**	**Non-solid or part solid**	**Management**
Category 1	Nodules containing fat or with a benign pattern of calcification are considered benign. Nodules < 15 mm^3 or if pleural or juxta pleural ≤ 3 mm. Including intrapulmonary nodules		No future action taken
Category 2	Intraparenchymal nodules with a volume of 15-49 mm^3. Pleural or juxtapleural nodules with a maximal diameter of 3.1-4.9mm.	Nodules with a maximal non-solid component diameter < 5 mm. Where there is a solid component, the component volume is <15 mm^3	Follow-up CT scan at 12 months
Category 3	Intraparenchymal nodules with a volume of 50-500 mm^3. Pleural or juxtapleural nodules with a maximal diameter of 5-9.9mm.	Nodules with a maximal non-solid component diameter 5 - 10 mm. Where there is a solid component, the component volume is 15-500 mm^3	Follow-up CT scan at 3 months and 12 months
Category 4	Intraparenchymal nodules with a volume of >500 mm^3. Pleural or juxtapleural nodules with a maximal diameter of ≥ 10 mm^3.	Nodules with a solid component with volume > 500 mm^3	Immediate referral to multidisciplinary team

Table 2 Numbers of patients and nodules per UKLS nodules categories 2, 3 and 4.

Nodule categories	Number of patients	Number of nodules
2	622	3065
3	333	1865
4	58	133

Table 3 Characteristics of UKLS screened participants with benign and malignant nodules

Characteristics	Benign nodules (n=961)	Malignant nodules (n=52)	*P*-values
Mean Age (years) ±SD	67.9±4.1	67.1±4.0	0.292
Gender			0.320
Male	707(73.6)	35(67.3)	
Female	254(26.4)	17(32.7)	
Smoking duration (years) ±SD	41.3±10.3	44.4±7.7	0.0229
Prior diagnosis of pneumonia[a]			0.520
No	561(58.4)	23(44.2)	
Yes	149(15.5)	8(15.4)	
Prior diagnosis of Bronchitis[b]			0.010
No	529(55.0)	18(34.6)	
Yes	223(23.2)	18(34.6)	
Prior diagnosis of asthma[c]			0.201
No	603(62.7)	26(50.0)	
Yes	126(13.1)	9(17.3)	
Prior diagnosis of tuberculosis[d]			0.716
No	634(66.0)	26(50.0)	
Yes	24(2.5)	0(0.0)	
Prior diagnosis of COPD[e]			0.080
No	605(63.0)	25(48.1)	
Yes	109(2.5)	9(17.3)	
Occupational exposure to asbestos[f]			0.269
No	526(58.9)	29(55.8)	
Yes	366(38.1)	14(26.9)	
Prior diagnosis of malignant tumour[g]			0.525
No	773(80.4)	40(76.9)	
Yes	187(19.5)	12(23.1)	
Family history of lung cancer[h]			0.028
No	721(75.0)	31(59.6)	
Early onset *	93(9.7)	10(19.2)	
Late onset*	146(15.2)	11(21.2)	
BMI (kg/m^2)	26.9±4.6	26.5±5.3	0.485
FEV1(Litres)	2.46±0.74	1.89±0.54	<0.0001
FVC (Litres)	3.49±0.92	2.63±0.67	<0.0001
Nodular volume (mm^3) (Median, IQR)	34.5 (21.0-70.5)	320.0 (49.5-1407.4)	<0.0001
Nodule counts	7.0±8.5	8.0±5.9	0.0193
Nodule location			0.583
Upper	573	33	
Middle or lower lobe	388	19	
Nodule type (solid as reference)			0.023
Nonsolid	947	49	
Part solid	4	3	

Abbreviations: (a, b, c, d, e, f, g, h indicates the percentage of missingness in covariates; a=26%, b=22%, c=24%, d=32%, e=26%, f=7.2%, g=0.1%, h=0.1%); COPD= chronic obstructive pulmonary disease. Family history early <60 years : late is 60 years and above.

Table 4 Regression coefficients, OR (95%CI) and SE for covariates in the final model for the probability of lung cancer in pulmonary nodules

Covariates	β-coefficient	Standard error	OR (95%CI)	***P*-values**
Intercept	-2.2915	1.2921	-	0.076
Age (years)	-0.0257	0.0174	0.975(0.942-1.008)	0.138
Gender (female)	0.5105	0.1653	1.666(1.205-2.304)	0.002
Asthma	-0.7777	0.2093	0.459(0.305-0.693)	<0.0001
Bronchitis	1.7616	0.2052	5.823(3.894-8.704)	<0.0001
Asbestos exposure	0.5884	0.1855	1.801(1.252-2.591)	0.002
Previous malignancy	0.5305	0.1824	1.699(1.189-2.430)	0.004
Family history of cancer				
Early onset *	1.9985	0.2158	7.378(4.834-11.262)	<0.0001
Late onset*	1.5724	0.2055	4.818(3.220-7.209)	<0.0001
Smoking duration (years)	0.0565	0.0097	1.059(1.038-1.078)	<0.0001
Forced vital capacity (Litres)	-1.1693	0.1108	0.311(0.250-0.386)	<0.0001
Nodule type (solid as reference)				
Nonsolid	1.6396	0.3370	5.153(2.662-9.976)	<0.0001
Part solid	0.4919	0.2837	1.635(0.938-2.852)	0.083
Nodule location				
Upper vs. middle or lower lobe	-0.1799	0.1607	0.835(0.610-1.144)	0.263
Nodular volume (mm^3)	0.000822	0.000186	1.001(1.000-1.001)	<0.0001

*Family history early <60 years: late is 60 years and above.

Note, Multiple imputations used in this analysis

Figure 1

The UKLS nodule care pathway management protocol

Reproduced from; Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess* 2016; **20**(40): 1-146.

Figure 2

Receiver operating curve for the UKLS Nodule risk model

References

1. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol* 2013; **14**(12): 1165-74.
2. Burki TK. The economic cost of respiratory disease in the UK. *Lancet Respir Med* 2017; **5**(5): 381.
3. Walters S, Benitez-Majano S, Muller P, et al. Is England closing the international gap in cancer survival? *Br J Cancer* 2015; **113**(5): 848-60.
4. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2015; **10**(7): 990-1003.
5. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007; **2**(8): 706-14.
6. Qi WX, Tang LN, He AN, Yao Y, Shen Z. Incidence and risk of treatment-related mortality in cancer patients treated with EGFR-TKIs: a meta-analysis of 22 phase III randomized controlled trials. *Respir Med* 2013; **107**(8): 1280-3.
7. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011; **365**(5): 395-409.
8. Baldwin DR, Duffy SW, Devaraj A, Field JK. Optimum low dose CT screening interval for lung cancer: the answer from NELSON? *Thorax* 2017; **72**(1): 6-7.
9. Callister ME, Baldwin DR, Akram AR, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015; **70 Suppl 2**: ii1-ii54.
10. McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. *N Engl J Med* 2013; **369**(10): 910-9.
11. Herder GJ, van Tinteren H, Golding RP, et al. Clinical prediction model to characterize pulmonary nodules: validation and added value of 18F-fluorodeoxyglucose positron emission tomography. *Chest* 2005; **128**(4): 2490-6.
12. Heuvelmans MA, Walter JE, Vliegenthart R, et al. Disagreement of diameter and volume measurements for pulmonary nodule size estimation in CT lung cancer screening. *Thorax* 2018; **73**(8): 779-81.
13. MacMahon H, Naidich DP, Goo JM, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. *Radiology* 2017; **284**(1): 228-43.
14. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009; **361**(23): 2221-9.
15. Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management protocol: modelling of a single screen randomised controlled trial of low-dose CT screening for lung cancer. *Thorax* 2011; **66**(4): 308-13.
16. Maisonneuve P, Bagnardi V, Bellomi M, et al. Lung cancer risk prediction to select smokers for screening CT--a model based on the Italian COSMOS trial. *Cancer Prev Res (Phila)* 2011; **4**(11): 1778-89.
17. Shen J, Liu Z, Todd NW, et al. Diagnosis of lung cancer in individuals with solitary pulmonary nodules by plasma microRNA biomarkers. *BMC Cancer* 2011; **11**: 374.
18. Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK. Development and Validation of Risk Models to Select Ever-Smokers for CT Lung Cancer Screening. *JAMA* 2016; **315**(21): 2300-11.
19. McRonald FE, Yadegarfar G, Baldwin DR, et al. The UK Lung Screen (UKLS): demographic profile of first 88,897 approaches provides recommendations for population screening. *Cancer Prev Res (Phila)* 2014; **7**(3): 362-71.
20. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess* 2016; **20**(40): 1-146.

21. Cassidy A, Myles JP, van Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. *Br J Cancer* 2008; **98**(2): 270-6.
22. van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol* 2006; **59**(10): 1102-9.
23. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res* 2011; **20**(1): 40-9.
24. Graham JW, Olchowski AE, Gilreath TD. How many imputations are really needed? Some practical clarifications of multiple imputation theory. *Prev Sci* 2007; **8**(3): 206-13.
25. Marcus MW, Chen Y, Raji OY, Duffy SW, Field JK. LLPi: Liverpool Lung Project Risk Prediction Model for Lung Cancer Incidence. *Cancer Prev Res (Phila)* 2015; **8**(6): 570-5.
26. Williams RL. A note on robust variance estimation for cluster-correlated data. *Biometrics* 2000; **56**(2): 645-6.
27. Royston P, Sauerbrei W. Interactions between treatment and continuous covariates: a step toward individualizing therapy. *J Clin Oncol* 2008; **26**(9): 1397-9.
28. Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med* 1997; **16**(9): 965-80.
29. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* 2010; **21**(1): 128-38.
30. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001; **54**(8): 774-81.
31. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; **15**(4): 361-87.
32. Schumacher M, Hollander N, Sauerbrei W. Resampling and cross-validation techniques: a tool to reduce bias caused by model building? *Stat Med* 1997; **16**(24): 2813-27.
33. Marcus MW, Field JK. Is Bootstrapping Sufficient for Validating a Risk Model for Selection of Participants for a Lung Cancer Screening Program? *J Clin Oncol* 2017; **35**(8): 818-9.
34. Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. *Arch Intern Med* 1997; **157**(8): 849-55.
35. Gould MK, Ananth L, Barnett PG, Veterans Affairs SCSG. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. *Chest* 2007; **131**(2): 383-8.
36. Al-Ameri A, Malhotra P, Thygesen H, et al. Risk of malignancy in pulmonary nodules: A validation study of four prediction models. *Lung Cancer* 2015; **89**(1): 27-30.
37. Perandini S, Soardi GA, Larici AR, et al. Multicenter external validation of two malignancy risk prediction models in patients undergoing 18F-FDG-PET for solitary pulmonary nodule evaluation. *Eur Radiol* 2017; **27**(5): 2042-6.
38. Schultz EM, Sanders GD, Trotter PR, et al. Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules. *Thorax* 2008; **63**(4): 335-41.
39. Han D, Heuvelmans MA, Oudkerk M. Volume versus diameter assessment of small pulmonary nodules in CT lung cancer screening. *Transl Lung Cancer Res* 2017; **6**(1): 52-61.
40. Mehta HJ, Ravenel JG, Shaftman SR, et al. The utility of nodule volume in the context of malignancy prediction for small pulmonary nodules. *Chest* 2014; **145**(3): 464-72.
41. Brenner DR, Boffetta P, Duell EJ, et al. Previous lung diseases and lung cancer risk: a pooled analysis from the International Lung Cancer Consortium. *Am J Epidemiol* 2012; **176**(7): 573-85.
42. Rosenberger A, Bickeboller H, McCormack V, et al. Asthma and lung cancer risk: a systematic investigation by the International Lung Cancer Consortium. *Carcinogenesis* 2012; **33**(3): 587-97.

43. Powell HA, Iyen-Omofoman B, Hubbard RB, Baldwin DR, Tata LJ. The association between smoking quantity and lung cancer in men and women. *Chest* 2013; **143**(1): 123-9.
44. Enomoto Y, Inui N, Kato T, et al. Low forced vital capacity predicts cytotoxic chemotherapy-associated acute exacerbation of interstitial lung disease in patients with lung cancer. *Lung Cancer* 2016; **96**: 63-7.
45. Field JK, Chen Y, Marcus MW, McRonald FE, Raji OY, Duffy SW. The contribution of risk prediction models to early detection of lung cancer. *J Surg Oncol* 2013; **108**(5): 304-11.

Figure1

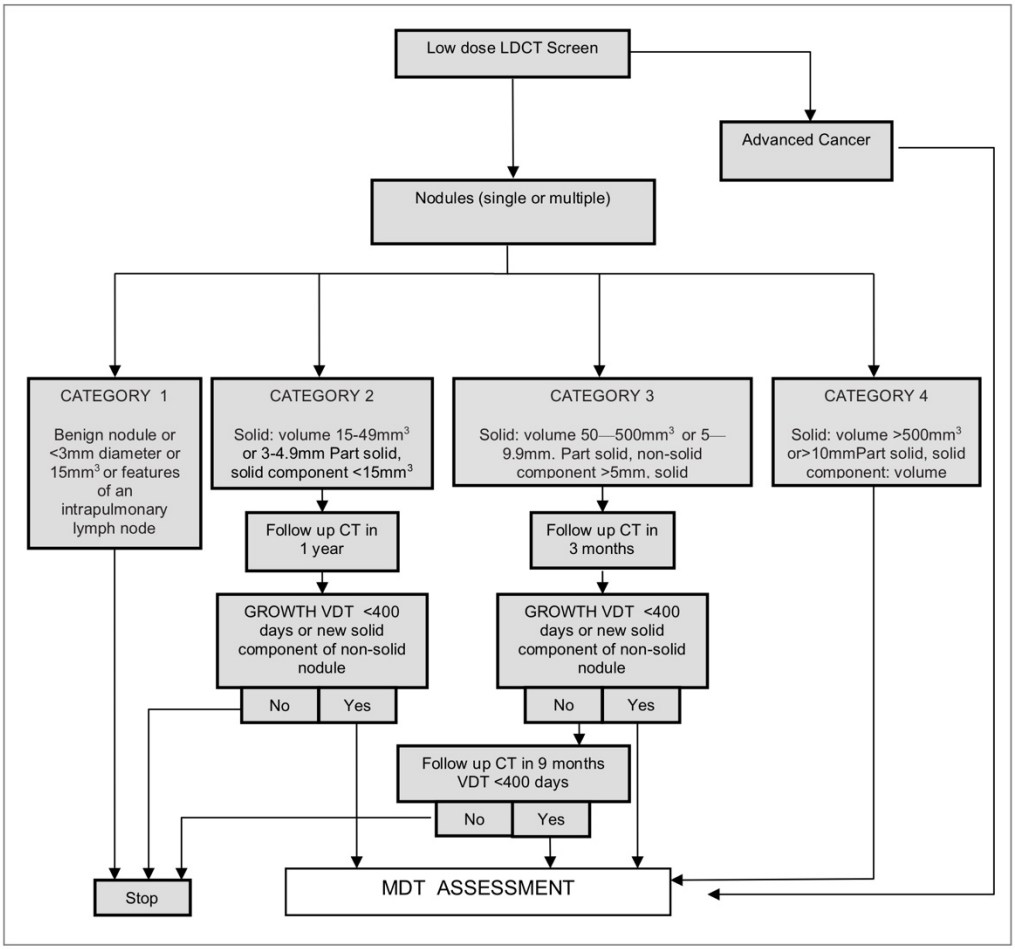
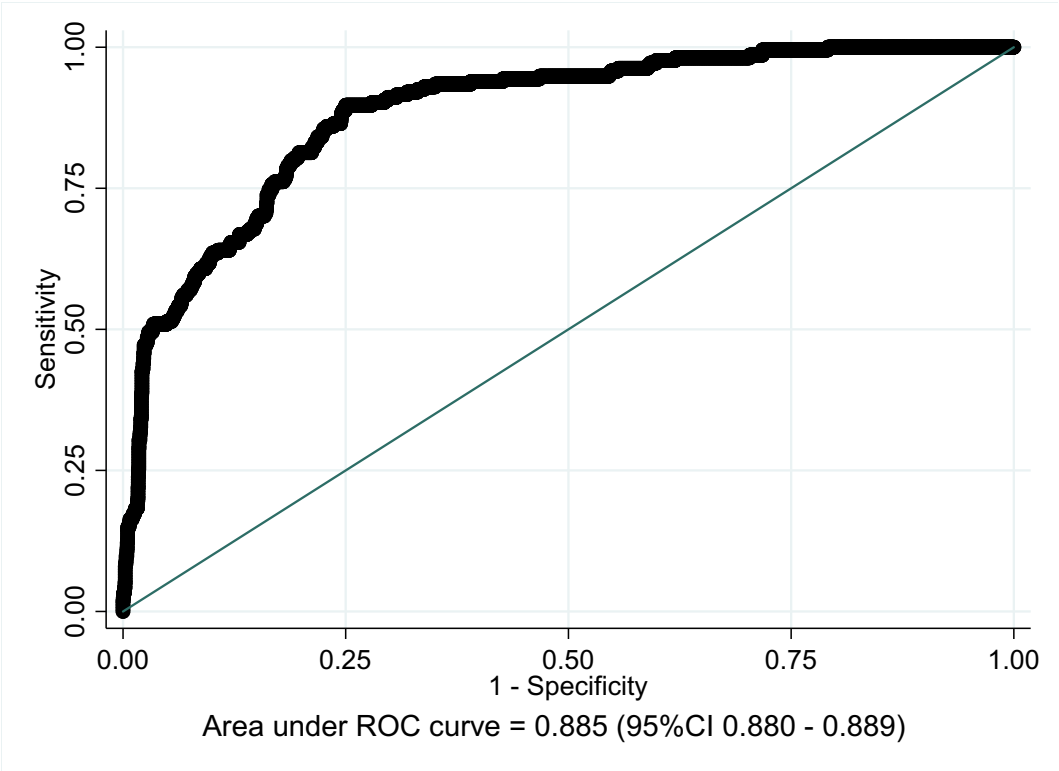

Low dose LDCT Screen
Advanced Cancer
Nodules (single or multiple)
CATEGORY 1
Benign nodule or <3mm diameter or 15mm3 or features of an intrapulmonary lymph node
CATEGORY 2
Solid: volume 15-49mm3 or 3-4.9mm Part solid, solid component <15mm3
CATEGORY 3
Solid: volume 50—500mm3 or 5—9.9mm. Part solid, non-solid component >5mm, solid
CATEGORY 4
Solid: volume >500mm3 or>10mmPart solid, solid component: volume
Follow up CT in 1 year
Follow up CT in 3 months
GROWTH VDT <400 days or new solid component of non-solid nodule
GROWTH VDT <400 days or new solid component of non-solid nodule
No
Yes
No
Yes
Follow up CT in 9 months VDT <400 days
No
Yes
Stop
MDT ASSESSMENT

Figure 2


Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity
0.00
0.25
0.50
0.75
1.00
Area under ROC curve = 0.885 (95%CI 0.880 - 0.889)