The effect of different radiological models on diagnostic accuracy and lung cancer screening performance

ABSTRACT

High false-positive (FP) scan rates associated with low-dose computed tomography (LDCT) lung cancer screening result in unnecessary follow-up tests and exposure to harm. The definition of a 'positive' scan can impact FP rates and screening performance. We explored the effect of Lung Imaging Reporting and Data System (Lung-RADS) criteria, PanCan Nodule Malignancy Probability Model and varying nodule size thresholds (≥ 4 mm, ≥ 6 mm, ≥ 8 mm) on diagnostic accuracy and screening performance compared with original trial definitions (National Lung Screening Trial (NLST) criteria) in a secondary analysis of a lung cancer screening cohort. We found Lung-RADS criteria and the PanCan Nodule Malignancy Probability Model could substantially improve screening performance and reduce FP scan rates compared with NLST definitions of positivity but that this needs to be balanced against possible risk of false-negative results.

Trial registration number Australian New Zealand Clinical Trials Registry, ACTRN1261000007033.

BACKGROUND

The landmark National Lung Screening Trial (NLST)¹ demonstrated lung cancer mortality reduction by low-dose computed tomography (LDCT) screening, paving the way for US Preventative Services Taskforce and Medicare screening recommendations. However, a major limitation of LDCT screening is the high positive scan rate, averaging 24.2% in NLST (threshold axial diameter ≥ 4 mm)¹; furthermore, over 95% of these nodules were benign.¹ Detected nodules require radiological follow-up creating a burden on healthcare systems and exposing participants to potential harm.

Strategies to improve this situation could include the following: (1) increasing the threshold nodule size, reflecting lower cancer risk in smaller nodules,^{2–3} (2) estimating the probability of malignancy using the PanCan multivariable Nodule Malignancy Probability Model (incorporating nodule size, location, attenuation, total count, spiculation, participant age, sex, family history of lung cancer and emphysema, henceforth referred to as the PanCan Model)⁴ and (3) categorisation using the

American College of Radiology Lung Imaging Reporting and Data System (Lung-RADS).⁵ The Lung-RADS classification is based on nodule average diameter, density and growth and also recommends the use of the PanCan Model to guide management of larger nodules (category 4B).

Larger nodule size thresholds are simple to implement but ignore other risk factors.^{2–3} The PanCan Model is more complex to administer but appears highly discriminatory^{4–7} and is recommended in British Thoracic Society guidelines⁸ (suggested cut-point for investigation $\geq 10\%$ risk). The Lung-RADS system is simple to use and improves false-positive rate (1–specificity, FPR) at the cost of lower sensitivity.^{9–10} Until now, no study has simultaneously compared these competing methods of nodule assessment on false-positive (FP) scan rates and other screening performance metrics.

AIM

To evaluate the impact of different definitions of positive scan results on screening performance by retrospective application of Lung-RADS, the PanCan Model and various nodule size thresholds to screening cohort data.

METHOD

Participant eligibility and recruitment have been described elsewhere.^{11–12} Two hundred and fifty-six healthy current or former smokers (171 men; 85 women) aged 60–74 years were enrolled in a LDCT screening study; median age 64.5 years; median pack-years of smoking 55 and 47% current smokers. Participants received baseline scans (T_0) and up to two annual incidence scans (T_1 and T_2) using a 64-detector helical CT based on NLST protocols. Criteria for scan positivity, based on NLST, were any nodule ≥ 4 mm diameter (baseline scan) and any new or growing nodule (incidence scan).^{11–12} Indeterminate nodules underwent 2 years radiological follow-up. Health status follow-up continued for 5 years. Data were censored 1 March 2016.

Scan results were reclassified using Lung-RADS (category 3 or 4 considered positive), the PanCan Model (full model with spiculation, $\geq 10\%$ risk considered positive) and increasing nodule size thresholds (exploratory cut-points set at maximum diameter of ≥ 4 mm, ≥ 6 mm or ≥ 8 mm and labelled d4, d6 and d8, respectively). Performance metrics were calculated at the participant level using the scan result and NLST Lung Cancer Status definition (cancer present; cancer absent¹³). Scans were excluded if cancer

status could not be determined (eg, participant lost to follow-up). Model discrimination, assessed using the area under the receiver operating characteristic curve (AUC), and calibration assessed by visual plot and Hosmer-Lemeshow test, were calculated at the nodule level.

95% CIs were calculated for sensitivity, specificity, positive predictive value and negative predictive value (Clopper-Pearson exact method¹⁴) and FP rate reduction (1000 bootstrapped samples). AUCs were estimated and compared non-parametrically using the method of Obuchowski which accounts for clustering of nodules within individuals and correlation between AUC comparisons.¹⁵ Statistical analysis was performed using R V3.2.4.

RESULTS

Baseline scans

Two hundred and fifty-six participants received T_0 scans (table 1); 136 participants had 301 nodules (median diameter 5.4 mm, range 4.0–34.0 mm). One hundred and twenty-eight (50.0%) scans were deemed positive (127 scans without historical images demonstrating nodule stability plus one scan with suspicious non-nodule findings). Lung cancer was diagnosed in five (2.0%) participants. One individual with missing lung cancer status was excluded. PanCan, Lung-RADS, d4, d6 and d8 correctly identified all participants with lung cancer. PanCan and d8 produced the greatest reduction in FP scans (89.4% reduction, 95% CI 83.6 to 95.2 and 78.0% reduction, 95% CI 69.4 to 86.6, respectively), improving specificity and positive predictive value without reducing sensitivity or negative predictive value (table 2).

Incidence scans

One hundred and fifty-six of 472 (33.1%) incidence scans (239 T_1 ; 233 T_2) were positive according to our original criteria (new nodule of any size or growth detected) (table 1). Lung cancer was diagnosed in three participants (1.3%) at T_1 and four (1.7%) at T_2 . Six individuals without lung cancer status were excluded. Increasing nodule size threshold for a positive scan result reduced FPR but also reduced sensitivity. Lung-RADS and d4 had similar performance characteristics (table 2).

Downstream effects

At baseline, the PanCan Model would have avoided 110/127 (86.6%) interval CT scans and 3/5 positron emission tomography (PET) scans in participants without cancer; Lung-RADS would have

avoided 75 interval CT scans and no PET scans. At the incidence rounds, The Queensland Lung Cancer Screening Study generated 229 interval CT scans from FP nodules and Lung-RADS would have reduced this number to 44. Across three rounds of screening, Lung-RADS would have avoided 260/356 (73.0%) interval CT scans, 2/7 (28.6%) PET scans and 2/3 (66.7%) bronchoscopies in participants without cancer. However, Lung-RADS would have misclassified one participant with lung cancer present at the T₂ screening round (tables 1 and 3).

Model performance

Ten baseline nodules in eight participants were diagnosed as lung cancer during follow-up (median 29.9 months, range 2.0–69.7). PanCan Model discrimination

was very good in the 301 baseline nodules (AUC 0.90; 95% CI 0.75 to 1) but not statistically different from Lung-RADS (AUC 0.84; 95% CI 0.69 to 0.98; difference in AUC=0.06, 95% CI –0.04 to 0.16, p value=0.25). Visual plot and Hosmer-Lemeshow goodness-of-fit test ($\chi^2=8.8$, df=8, p=0.36) did not indicate significant miscalibration.

DISCUSSION

As lung cancer screening gains traction internationally, attention focuses on minimising harm and controlling costs by reducing FP scan rates. In this exploratory comparative study, stricter definitions of positivity decreased FP results, improved performance metrics and reduced downstream tests at the risk of increasing false-negative scans at the incidence round.

At baseline, all methods were highly sensitive. Increasing nodule size thresholds and Lung-RADS improved specificity to 76–89%, but the PanCan Model had the highest specificity of 94.8%. At incidence scan rounds, stricter size definitions improved specificity and reduced FP scans at the cost of lower sensitivity. FPR was reduced by a similar degree to that seen in a retrospective application of Lung-RADS to NLST data (52–89% and 74–92% reduction at baseline and incidence rounds, respectively, compared with 52% and 76%, respectively¹⁰).

Since baseline scans have no historical comparison against which to assess growth, they inherently generate more positive scans and downstream tests than incidence scans.¹ In contrast, incident nodules are more likely to be malignant.¹⁶ In the absence of a validated multivariable risk model for incidence scans, a more conservative, smaller size threshold compared with the baseline scan, such as recommended by Lung-RADS, seems prudent. However, defining an optimal threshold at prevalence and incidence rounds goes beyond the pure metrics of the test and requires a health economic perspective which may differ between countries and healthcare settings. All measurements in this study were based on maximum axial diameter yet volumetric nodule analysis reportedly gives a more accurate assessment of size and interval growth. The NELSON trial compared diagnostic accuracy between diameter-based management and volume-based management and found similar sensitivity but higher specificity for a volumetric approach¹⁷ (diameter sensitivity 92.4% and specificity 90.0%; volumetry sensitivity 90.9% and specificity 94.9%). The diameter measurements were generated from volumetric software results and it is possible this may have underestimated the true difference by avoiding the variability associated with human reader measurements. The true advantage of volumetry, which requires specialised software analysis, against a multivariable risk assessment merits further investigation.

Our study is the first to simultaneously compare these differing methods of scan classification. It has limitations inherent to retrospectivity and relatively small cohort size; however, participants were well characterised and long, near-complete follow-up made cancer status misclassification unlikely.

In conclusion, we demonstrate lung cancer screening performance and FP scan rate can be improved by varying the definition of a positive scan balanced against

Table 1 Lung cancer screening scan results: comparison of Queensland Lung Cancer Screening Study original definitions, Lung-RADS criteria, PanCan Model and differing nodule size thresholds

Baseline round	Positive*		Negative			
d4	128 (50.0)	CT scans n=256 (100.0)	128 (50.0)			
d6	64 (25.0)		192 (75.0)			
d8	32 (12.5)		224 (87.5)			
Lung-RADS	56 (21.9)		200 (78.1)			
PanCan Model	18 (7.0)		238 (93.0)			
	TP	FP	NA	TN	FN	NA
d4	5 (2.0)	123 (48.0)	0 (0.0)	127 (49.6)	0 (0.0)	1 (0.4)
d6	5 (2.0)	59 (23.0)	0 (0.0)	191 (74.6)	0 (0.0)	1 (0.4)
d8	5 (2.0)	27 (10.5)	0 (0.0)	223 (87.1)	0 (0.0)	1 (0.4)
Lung-RADS	5 (2.0)	51 (19.9)	0 (0.0)	199 (77.7)	0 (0.0)	1 (0.4)
PanCan Model	5 (2.0)	13 (5.1)	0 (0.0)	237 (92.6)	0 (0.0)	1 (0.4)
Incidence rounds	Positive		Negative			
d-All	156 (33.1)	CT scans n=472 (100.0)	316 (66.9)			
d4	44 (9.3)		428 (90.7)			
d6	26 (5.5)		446 (94.5)			
d8	17 (3.6)		455 (96.4)			
Lung-RADS	46 (9.7)		426 (90.3)			
	TP	FP	NA	TN	FN	NA
d-All	7 (1.5)	149 (31.6)	0 (0.0)	310 (65.7)	0 (0.0)	6 (1.3)
d4	7 (1.5)	37 (7.8)	0 (0.0)	422 (89.4)	0 (0.0)	6 (1.3)
d6	5 (1.1)	21 (4.4)	0 (0.0)	438 (92.8)	2 (0.4)	6 (1.3)
d8	5 (1.1)	12 (2.5)	0 (0.0)	447 (94.7)	2 (0.4)	6 (1.3)
Lung-RADS	6 (1.3)	39 (8.3)	1 (0.2)	420 (89.0)	1 (0.2)	5 (1.1)

Baseline (T0) and incidence (T1 and T2) screening rounds.

Data presented as count (%).

Criteria for positive baseline scan: d4 ≥4 mm threshold; d6 ≥6 mm threshold; d8 ≥8 mm threshold; Lung-RADS, Lung Imaging Reporting and Data System categories 3–4 and PanCan Model–Pan-Canadian multivariable logistic-regression risk model threshold ≥10%.

Criteria for positive incidence scan: d-All new or growing nodule(s) of any size; d4 ≥4 mm threshold; d6 ≥6 mm threshold; d8 ≥8 mm threshold and Lung-RADS categories 3–4.

*One baseline scan was positive due to non-nodule suspicious findings.

FN, false negative; FP, false positive; NA, not assessed; TN, true negative; TP, true positive.

Table 2 Lung cancer screening scan performance metrics: comparison of Queensland Lung Cancer Screening Study original definitions, Lung-RADS criteria, PanCan Model and differing nodule size thresholds

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	FPR reduction (%)
Baseline scan					
d4	100 (47.8 to 100)	50.8 (44.4 to 57.2)	3.9 (1.3 to 8.9)	100 (97.1 to 100)	NA
d6	100 (47.8 to 100)	76.4 (70.6 to 81.5)	7.8 (2.6 to 17.3)	100 (98.1 to 100)	52.0 (39.4 to 64.6)
d8	100 (47.8 to 100)	89.2 (84.7 to 92.8)	15.6 (5.3 to 32.8)	100 (98.4 to 100)	78.0 (69.4 to 86.6)
Lung-RADS	100 (47.8 to 100)	79.6 (74.1 to 84.4)	8.9 (3.0 to 19.6)	100 (98.2 to 100)	58.5 (46.5 to 70.5)
PanCan Model	100 (47.8 to 100)	94.8 (91.3 to 97.2)	27.8 (9.7 to 53.5)	100 (98.5 to 100)	89.4 (83.6 to 95.2)
Incidence scan					
d-All	100 (59.0 to 100)	67.5 (63.0 to 71.8)	4.5 (1.8 to 9.0)	100 (98.8 to 100)	NA
d4	100 (59.0 to 100)	91.9 (89.1 to 94.3)	15.9 (6.6 to 30.1)	100 (99.1 to 100)	75.2 (67.0 to 83.4)
d6	71.4 (29.0 to 96.3)	95.4 (93.1 to 97.1)	19.2 (6.6 to 39.4)	99.5 (98.4 to 99.9)	85.9 (79.4 to 92.4)
d8	71.4 (29.0 to 96.3)	97.4 (95.5 to 98.6)	29.4 (10.3 to 56.0)	99.6 (98.4 to 99.9)	91.9 (87.2 to 96.6)
Lung-RADS	85.7 (42.1 to 99.6)	91.5 (88.6 to 93.9)	13.3 (5.1 to 26.8)	99.8 (98.7 to 100)	73.8 (64.9 to 82.7)

Baseline (T0) and incidence (T1 and T2) screening rounds.

Data presented as percentage (95% CI). Lung-RADS, Lung Imaging Reporting and Data System categories 3–4; PanCan Model, Pan-Canadian multivariable logistic-regression risk model threshold $\geq 10\%$; d4, d6, d8, size threshold definitions for positive scan—the presence of at least one nodule with maximum axial diameter ≥ 4 mm, ≥ 6 mm and ≥ 8 mm, respectively.

At baseline scan, d4 was the definition used in the Queensland Lung Cancer Screening Study; d-All, Queensland Lung Cancer Screening Study definition of positive scan during incidence round—new or growing nodule of any size.

FPR, false-positive rate; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

Table 3 Downstream tests generated from false-positive (FP) scan results

	Threshold/method					
	d-All	Lung-RADS	PanCan	d4	d6	d8
Baseline round, FP	123	51	13	—	59	27
Interval CT	127	52	17	—	63	31
CT-guided biopsy	3	3	3	—	3	3
PET or PET-CT	5	5	2	—	5	5
Bronchoscopy	1	1	1	—	1	1
Incidence rounds, FP	149	39	—	37	21	12
Interval CT	229	44	—	65	37	23
CT-guided biopsy	0	0	—	0	0	0
PET or PET-CT	2	0	—	2	2	2
Bronchoscopy	2	0	—	2	2	2

Criteria for positive baseline scan: d4 ≥ 4 mm threshold; d6 ≥ 6 mm threshold; d8 ≥ 8 mm threshold; Lung-RADS, Lung Imaging Reporting and Data System categories 3–4 and PanCan Model—Pan-Canadian multivariable logistic-regression risk model threshold $\geq 10\%$.

Criteria for positive incidence scan: d-All new or growing nodule(s) of any size; d4 ≥ 4 mm threshold; d6 ≥ 6 mm threshold; d8 ≥ 8 mm threshold and Lung-RADS categories 3–4.

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possible false-negative results. At baseline, the PanCan Model yielded best results, whereas at incidence scan, d4 followed by Lung-RADS yielded the best specificity and sensitivity.

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